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**Lithiation—Borylation Methodology**

*Applications in the Synthesis of Polypropionate Fragment and Polyfluoromethylation Reactions of Organoboronic Esters*

# Lithiation–Borylation Methodology: Applications in the Synthesis of Polypropionate Fragment and Polyfluoromethylation Reactions of Organoboronic Esters


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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

University of Bristol, School of Chemistry

November 2018

# Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirement of the University’s *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by a specific reference in the text, the work is the candidate’s own work. Any views express in the dissertation are those of the author.

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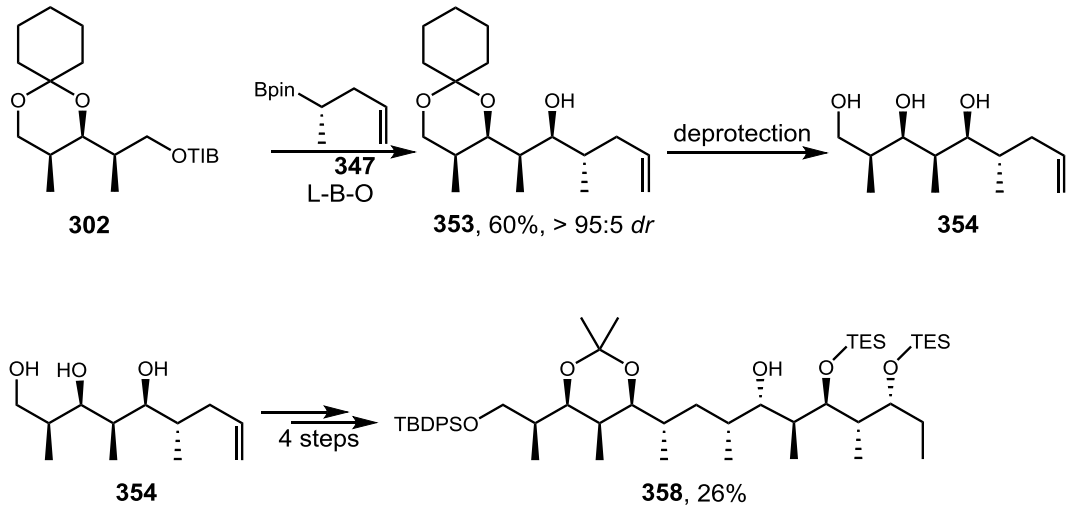
# Abstract

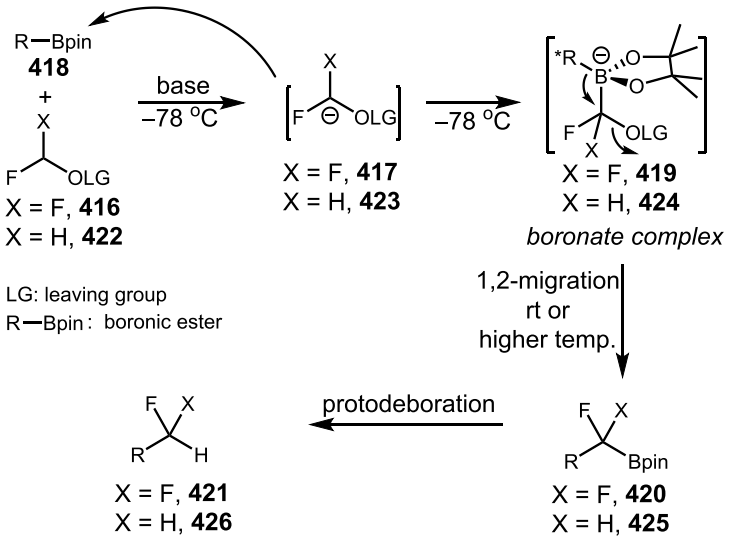
The thesis describes the applications of lithiation–borylation methodology in polypropionate synthesis and the synthesis of organofluorine compounds.

Firstly, an efficient method for the synthesis of polypropionate fragments based on building block assembly strategy using lithiation–borylation reaction has been developed. Benzoate ester **302** can react with boronic ester **347** efficiently via lithiation-borylation reaction and subsequent oxidation to afford alcohol **353** in good yield and with excellent diastereoselectivity, which can be applied in the synthesis of polypropionate fragment **358**, a key intermediate of 6-deoxyerythronolide (Scheme A). Some limitations, such as substrate control and O-migration, were observed in the reaction process.




**Scheme A.** Synthesis of polypropionate fragment based on building block assembly strategy using lithiation–borylation methodology.

Secondly, we extensively explored the introduction of difluoromethyl and monofluoromethyl groups by lithiation–borylation reaction with organoboronic esters (Scheme B). The difluoromethylation and monofluoromethylation reactions proved to be very challenging due to the instability of *in situ* generated fluorinated carbanion **417** or **423**. Generally, the formation of boronate complex **419** or **424** was not detected. Additionally, we proposed some other strategies for the future work.




**Scheme B.** Exploration of the difluoromethylation and monofluoromethylation reactions of organoboronic esters using lithiation–borylation methodology.

# Acknowledgements

Firstly, I would like to express my special appreciation and thanks to my supervisor Professor Varinder K. Aggarwal for giving me the opportunity of undertaking my PhD study in his group. I am grateful for the guidance and support he has given to me over the past four years. It has been a great honour to work in such an excellent international group. I would also like to thank Dr. Eddie Myers and Dr. Adam Noble, the past and present research officers of the group, for their additional help and support. I wish to express my gratitude, as a member of EPSRC Centre for Doctoral Training (CDT) in Chemical Synthesis, to the staff Professor Kevin Booker-Milburn, Dr. Emma Rose, Ms. Mar Ruiz and Dr. Laura Chavda for all the service and help they provided. Additionally, I would like to thank the University of Bristol and EPSRC for funding.

It has been a great pleasure to be a part of the Aggarwal group, and I deeply appreciate its friendly, stimulating and supportive atmosphere. I wish to thank all the past and present members of the group with whom I have many precious memories. I warmly thank all the members of lab N214 for making the daily lab work such an enjoyable experience. A great many thanks to Joe Bateman, Lydia Dewis and Dr. Hsuan-Hung Liao for proofreading my thesis.

I would like to show my appreciation to my former flatmates in Bristol, Dr. Xu Liu and Miss Yue Lang, for making me feel at home in this grey and rainy country which is far from my hometown in China. It is an absolute privilege sharing with you many good happy days that I will always cherish and bear in mind. I would also like to thank all other Chinese friends, Professor Yahui Wang, Dr Jingjing Wu, Dr. Changcheng Jing, Professor Lin He and Dr. Hsuan-Hung Liao, I really enjoy the time spending with you, especially the hot-pot dinners.

I owe special thanks to my girlfriend, Miss Mengmeng Zhao, for your tons of love. It is my great luck to meet you in this world. You are unique and one of a kind in my world, your presence is a precious present and your love means so much to me. I know I am always with you no matter where we are.

My deepest and warmest acknowledgements go to my parents. Words cannot express how grateful I am to my beloved mother, Mrs Lanzhen Zhou, and father, Mr Guangli Zhou, for all the unconditional love and support. Seeking a PhD degree in the United Kingdom makes me absent at many occasions. I miss the time when we are together. Your prayer for me is what sustains me thus far. Love you.

# Abbreviations

| | |
|---|---|
| aq | *aqueous* |
| Ar | *aromatic group* |
| brs | *broad singlet (spectral)* |
| BuLi | *butyllithium* |
| cat. | *catalytic/catalyst* |
| Cb | *diisopropyl carbamate* |
| CPME | *cyclopentyl methyl ether* |
| Cy | *cyclohexyl* |
| d | *doublet (spectral)* |
| dd | *doublet of doublet (spectral)* |
| ddd | *doublet of doublet of doublet (spectral)* |
| dddd | *doublet of doublet of doublet of doublet (spectral)* |
| DIBAL | *diisobutylaluminium hydride* |
| DMAP | *N,N-dimethyl-4-aminopyridine* |
| d.e. | *distereomeric excess* |
| dq | *doublet of quartet (spectral)* |
| d.r. | diastereomeric ratio |
| dt | *doublet of triplet (spectral)* |
| δ | *chemical shift (ppm)* |
| e.e. | *enantiomeric excess* |
| EI | *electron impact* |
| ESI | *electrospray ionization* |
| eq | *equivalents* |
| e.r. | *enantiomeric ratio* |
| e.s. | *enantiomeric specificity* |
| GCMS | *Gas Chromatography - Mass Spectrometry* |
| GP | *general procedure* |
| hept | *heptet* |
| hr(s) | *hour(s)* |
| HRMS | *high resolution mass spectrum (spectral)* |
| IR | *infrared* |
| *J* | *coupling constant (spectral)* |
| KHMDS | *potassium bis(trimethylsilyl)amide* |
| LDA | *lithium diisopropylamide* |

| | |
|---|---|
| LHMDS | *lithium bis(trimethylsilyl)amide* |
| lit. | *literature* |
| LiTMP | *lithium tetramethylpiperidine* |
| M | *molar* |
| m | *multiplet (spectral)* |
| Me | *methyl* |
| MHz | *megahertz* |
| min | *minute(s)* |
| NaHMDS | *sodium bis(trimethylsilyl)amide* |
| mol | *mole* |
| mp | *melting point* |
| MS | *mass spectrometry* |
| m/z | *mass to charge ratio (spectral)* |
| NMR | *nuclear magnetic resonance* |
| Nu | *nucleophile* |
| pin | pinacol |
| ppm | *parts per million* |
| q | *quartet (spectral)* |
| R | *any alkyl group* |
| $R_f$ | *retention factor* |
| rt | *room temperature* |
| s | *singlet (spectral)* |
| sp | *sparteine* |
| t | *triplet (spectral)* |
| T | *temperature* |
| TBS | *tert-butyl dimethyl silane* |
| TBDPS | *tert-butyl diphenyl silane* |
| td | *triplet of doublet (spectral)* |
| Tf | *trifluoromethanesulfonyl* |
| THF | *tetrahydrofuran* |
| TIB | Triisopropyl benzoate |
| TMEDA | *N,N,N′,N′-Tetramethylethylenediamine* |

# Table of Contents

# 1. Introduction

Organoboron reagents have found a wide variety of applications in synthetic chemistry owing to the opportunity of converting them into a broad range of functional groups, producing various kinds of molecules with excellent enantiopurity (see §.1.4). All transformations generally originate from the nucleophilic substitution of a boron atom, which are followed by a 1,2-metalate rearrangement.[1-2] Amongst various metals and semimetals, boron appears capable of organising the course of the reaction with high stereochemical control. In 1961 Herbert C. Brown reported the creative work on the first nonenzymatic asymmetric hydroboration of alkenes,[3-4] and since then an increasing number of methods have been reported for the transformation of various functionalities. The main disadvantage of boranes (Figure 1.1a), is that they are usually sensitive to air and moisture, thus resulting in difficulty in manipulation. In sharp contrast, boronic esters (Figure 1.1b), are much more stable. The increased stability can be accounted for by the electron π-donation from the oxygen lone pairs to the empty p-orbital on the boron atom, rendering the atom less electrophilic and thus less likely to decompose.

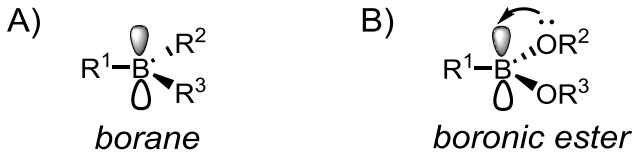


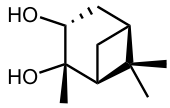

**Figure 1.1** Differences between boranes and boronic esters

A variety of strategies have been developed for the asymmetric synthesis of secondary and tertiary boronic esters, demonstrating the great value and magnitude of organoboronic esters in modern organic synthesis.[5]

In this chapter, the methods of lithiation–borylation, which are powerful in asymmetric homologation of boronic esters, have been summarised. Alternative stereospecific conversion of enantioenriched secondary and tertiary boronic esters will also be briefly described.

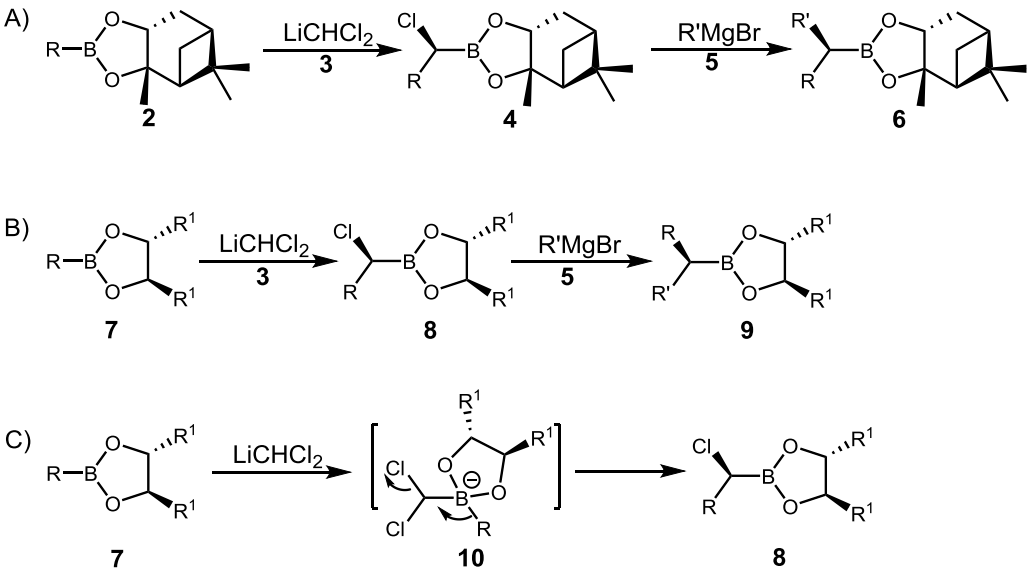
## *1.1. Matteson Homologation of Boronic Esters*

Matteson and coworkers have developed methodologies for the homologation of chiral boronic esters, a milestone contribution in the field of asymmetric synthesis.[6-12] In 1980s, they reported the direct chiral synthesis of boronic esters using (+)-(*1S,2S,3R,5S*)-pinanediol **1** as chiral director.[6-9] In this approach, dichloromethyl lithium, generated either from treatment of dichloromethane with butyllithium at –100 $^{o}$C or addition of LDA to a mixture of dichloromethane and boronic ester **2** below –30 $^{o}$C, reacted with boronic ester **2** to generate asymmetric α-alkyl organoboron compound **4**, followed by the addition of Grignard reagent **5** to produce the homologated boronic ester **6**. Boronic ester **7** with the $C_2$-symmetrical diol auxiliary was effective at providing chiral boronic ester **9** via a similar procedure.




(+)-(*1S,2S,3R,5S*)-pinanediol, **1**

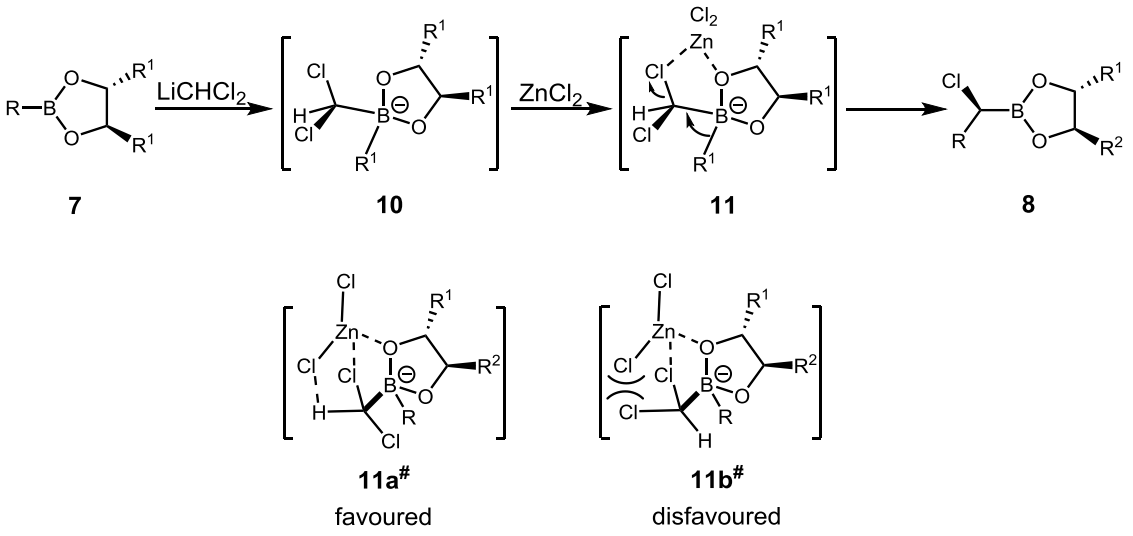
**Figure 1.2** Matteson chiral director.




**Scheme 1.1.** Matteson homologation reactions and the general mechanism.

The general mechanism of the Matteson homologation was shown in Scheme 1.1C. The reaction is based on a key intermediate boronate complex **10**, which is generated from

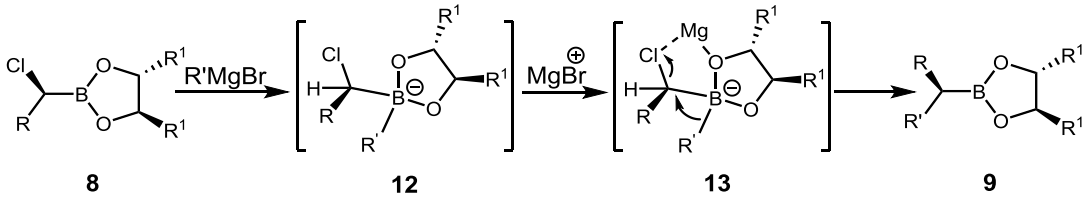
the nucleophilic addition of dichloromethyl lithium to enantioenriched boronic ester **7**. Sequentially, the homologated boronic ester **8** was delivered via 1,2-metalate rearrangement upon warming the reaction to ambient temperature. High levels of stereoselectivity were observed during the 1,2-migration owing to the presence of the chiral ligand on boron centre. It is noteworthy that addition of the Lewis acid, $ZnCl_2$, also helps control the excellent stereoselection.[8] Corey and co-workers suggested that the coordination of zinc cation to both the oxygen atom on boron and chlorine atom of dichloromethyl as well as a hydrogen bond between chloride and proton (see **11a**$^{\#}$) make **11** the most favourable transition state among all 4 possible transition states, which, after 1,2-migration, leads to the observed predominating diastereomer **8** (Scheme 1.2).[13] Using ab initio calculations, Midland and coworkers investigated the transition state for Matteson homologation, to rationalise the observed stereoselectivity.[14] They demonstrated that transition state **11a**$^{\#}$ (Scheme 1.2) where the metal cation is coordinated to the less sterically congested oxygen with the nonparticipating chlorine *anti* to the metal is the lowest energy transition state. Their computational work confirmed the above analysis.[14]




**Scheme 1.2.** Transition states analysis of Matteson homologation.

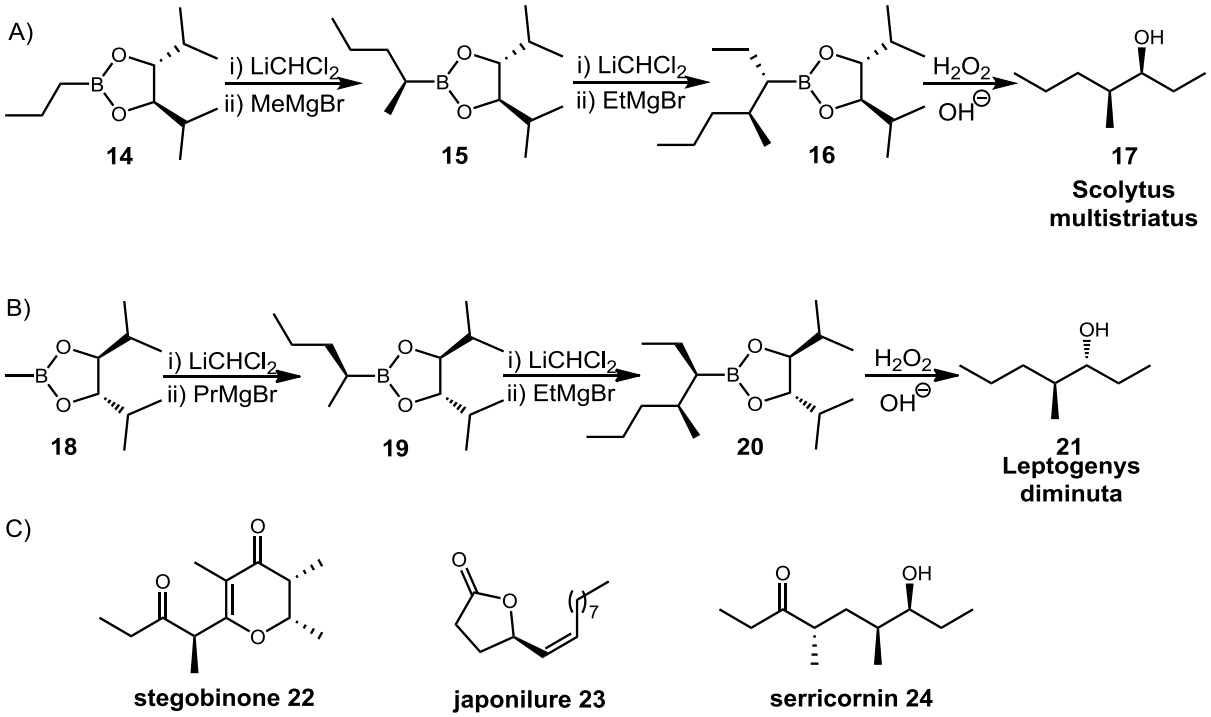
The chlorinated boronic ester **8** can further react with a Grignard reagent at cryogenic temperatures, generating boronate complex **12**, where the R group is placed in the position previously occupied by the noncoordinating chlorine of **10**. Transition state **13**

encounters the same relative group sizes as transition state **11**, delivering further homologated boronic ester **9** via a similar 1,2-metalate migration (Scheme 1.3).



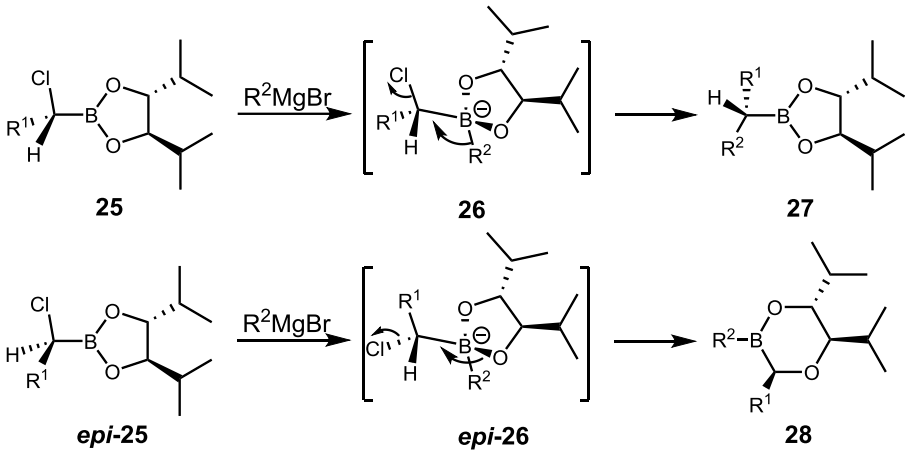

**Scheme 1.3.** Homologation of α-chloro boronic esters.

The power and potential of the Matteson homologation was showcased by Matteson and coworkers by applying the reaction in the synthesis of a series of natural products. For instance, the stereocontrolled synthesis of a pair of diastereomeric insect pheromones **17** and **21** was achieved via Matteson homologation.[15] (*4R,5R*)-(4,5-Diisopropyl-2-propyl)-1,3,2-dioxaborolane **14** underwent homologation and methylation affording **15**, which was further converted to **16** via homologation and ethylation (Scheme 1.4). Subsequent peroxidic oxidation produced **17**, a component of the aggregation pheromone of the elm bark beetle *Scolytus multistriatus* (Scheme 1.4A). (*4S,5S*)-(4,5-Diisopropyl-2-methyl)-1,3,2-dioxaborolane **18** reacting with dichloromethyl lithium followed by addition of propylmagnesium bromide generated **19**, which possesses the same (*S*)-configuration in the 2-pentyl group as **15** but the opposite configuration of chiral director. Transformation of **19** via homologation and ethylation delivered diastereomer **20**, which was oxidised to (*3R,4S*)-4-methyl-3- heptanol **21**, the trail pheromone of the Southeast Asian ponerine ant *Leptogenys diminuta* (Scheme 1.4B). The excellent diastereoselectivity was determined by $^{13}C$ NMR spectroscopy and the ratios of **17** and **21** were as high as 700:1 and 1:500 respectively. Additionally, some other natural products, such as stegobinone **22**,[16-17] japonilure **23**,[18] and serricornin **24**[19] have also been synthesised using the Matteson homologation (Scheme 1.4C).




**Scheme 1.4.** Applications of Matteson homologation in natural products synthesis.

In spite of its great power, the Matteson homologation has not been widely adopted, due to some existing limitations. In some cases, a pair of diastereomeric boronic esters behave differently when reacting with the same organometallic reagent. For example, the treatment of boronic ester **25** with a Grignard reagent afforded the desired homologated product **27** via intermediate boronate complex **26** (Scheme 1.5). In contrast, the treatment of the diastereomeric ester ***epi*-25** with the same reagent only gave borinic ester **28**.[20] Boronate complex ***epi*-26** was presumably generated in course, however, the more favourable conformation is the one placing group $R^1$ *anti* to group $R^2$, requiring one oxygen atom of boronic ester arranged *antiperiplanar* to the chlorine. Thus, the 'ate' complex became more prone to undergo O-migration instead of C-migration, generating ring-expanded product **28**.




**Scheme 1.5.** Matteson homologation with diastereomeric boronic esters.

Another disadvantage may lie in the operation complexity during iterative homologation process. Since the created stereogenic centre is dictated by the chirality of the diol of the boronic ester, when the opposite stereoisomer is needed, additional steps will be required to invert the diol stereochemistry. This procedure includes the cleavage of the diol after the first homologation to release the corresponding boronic acid, and subsequent esterification with the appropriate diol to access the required stereochemistry, which can further undergo the second homologation.

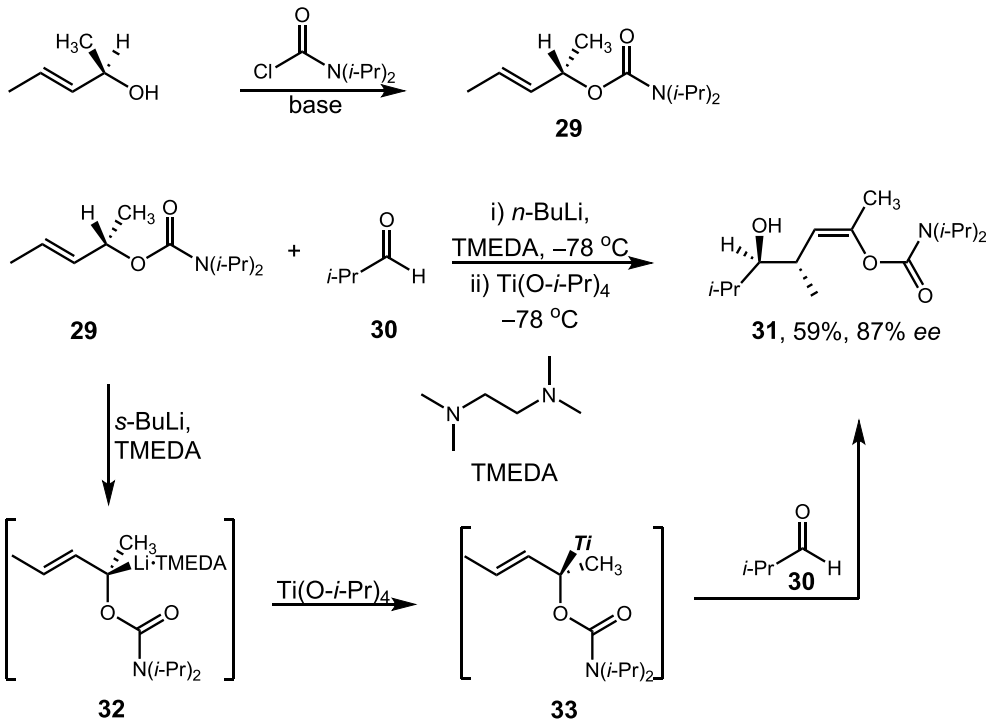
The methodology is not useful for the preparation of chiral tertiary boronic esters due to the low stereoselection and low predictability during the reaction course.[21]

## *1.2. Hoppe-type Carbamates*

To overcome the limitations of Matteson homologation, a potentially more powerful and efficient strategy is to utilise reagent control in place of substrate control in the reaction process. This methodology requires a carbenoid that is configurationally and chemically stable to the reaction conditions and sufficiently reactive to effectuate the homologation of boronic esters. Aggarwal and coworkers discovered that chiral sulfur ylides can undergo effective homologations with a variety of organoboranes with excellent stereoselectivity.[22-23] However, the high efficiency is limited to boranes, and the sulfur ylides cannot react with boronic esters due to the increased barrier of migration of the corresponding 'ate' complex. Blakemore and coworkers reported the

utility of Hoffmann's α-chloro Grignard reagents and the corresponding lithium derivatives to the iterative homologation process. The chlorosulfoxide precursors were synthesised via a two-step procedure, however some racemisation took place over the homologation course.[242]

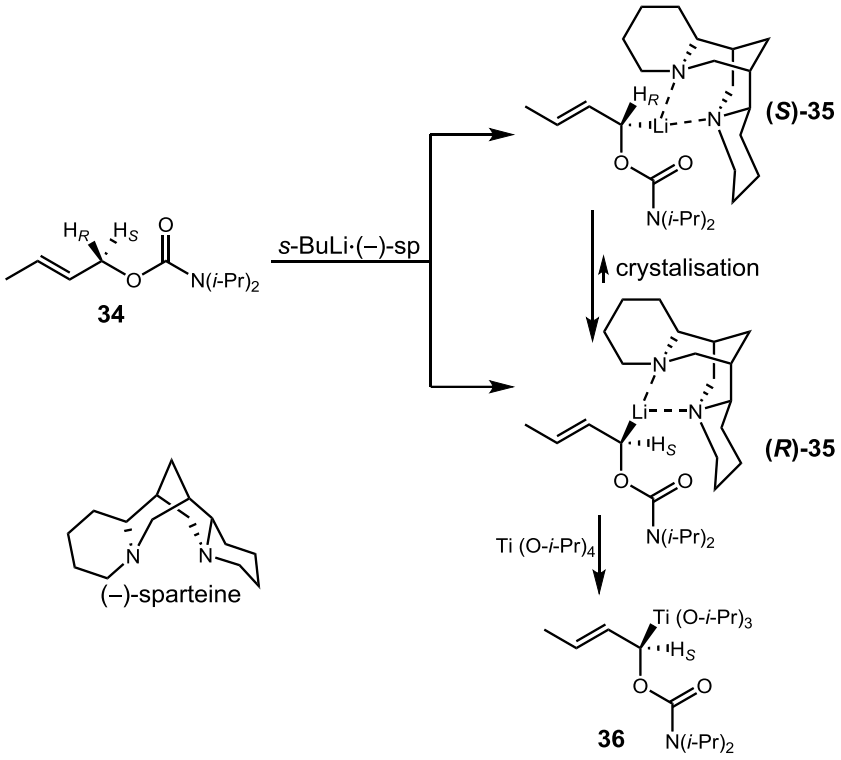
### 1.2.1. Hoppe-type Diisopropyl Carbamates




**Scheme 1.6.** Hoppe's homoaldol reaction with 2-alkenyl diisopropylcarbamate.

Alternatively, Hoppe-type lithiated carbamates are another class of chiral carbenoids, which are more readily accessible, and fulfil the criteria for the homologation of boronic esters. In 1980s, Hoppe and coworkers reported the application of secondary 2-alkenyl diisopropylcarbamate **29**, prepared from the corresponding crotyl alcohol and carbamoyl chloride, in the homoaldol reaction with aldehyde.[24] They established that carbamate **29** (84% *ee*) can be deprotonated by *n*-BuLi and TMEDA with configurational retention at –78 °C, subsequent lithium-titanium exchange gives complex **33** with configurational retention, which can further react with aldehyde **30** affording only one diastereoisomer **31** in 59% yield and 87% *ee*.[24] The result demonstrated that lithiated carbamate **32** was configurationally stable at cryogenic

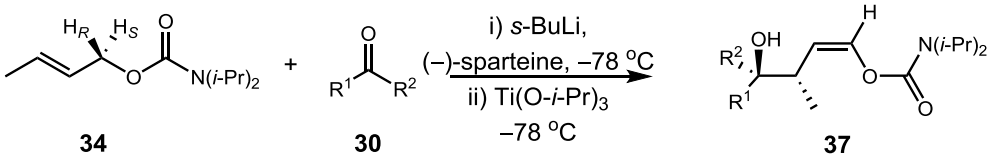
temperature (below −70 °C), which was furthered confirmed by the $t_{1/2}$ of racemisation ($t_{1/2} \geq 7$ hrs). (Scheme 1.6).




**Scheme 1.7.** Hoppe's secondary allyllithium generated from primary carbamate.

Primary allyl carbamates were also exploited by Hoppe and coworkers.[25] Lithiated carbamate **35**, generated from deprotonation of carbamate **34**, was found to be configurationally labile. Second-order asymmetric induction in the presence of (–)-sparteine resulted in the crystallisation of only one enantiomer (*R*)-**35**, which was transmetalated to the configurationally stable titanium derivative **36** (Scheme 1.7). The subsequent addition to achiral aldehydes **30a-i** and ketone **30j** gave diastereomerically pure adducts **37a-j** in 62%-95% yield and with 80%-95% enantiomeric excess (Table 1.1).[25]

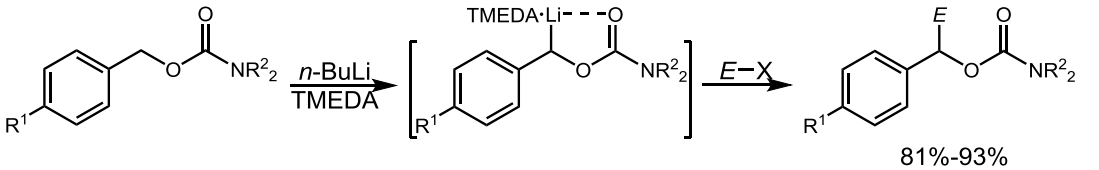
**Table 1.1.** Hoppe's homoaldol reaction with 2-alkenyl diisopropylcarbamate.




**34** **30** **37**

| **37** | **R¹** | **R²** | **Yield (%)** | ***ee* (%)** |
|---|---|---|---|---|
| **a** | $(CH_3)_2CH$ | H | 90 | 90 |
| **b** | $CH_3$ | H | 95 | 80 |
| **c** | $CH_3C(CH2)_2$ | H | 93 | 84 |
| **d** | $(CH_3)_2C=CH-CH_2$ | H | 62 | 92 |
| **e** | $H_2C=CCH_3$ | H | 78 | 86 |
| **f** | $H_2C=C$-*i*-Pr | H | 81 | 90 |
| **g** | *n*-$C_4H_9$ | H | 92 | 82 |
| **h** | (*R*)-$CH_3CH(OBn)$ | H | 79 | >95 |
| **i** | (*S*)-$CH_3CH(OBn)$ | H | 90 | >95 |
| **j** | $CH_3$ | $CH_3$ | 92 | 82 |

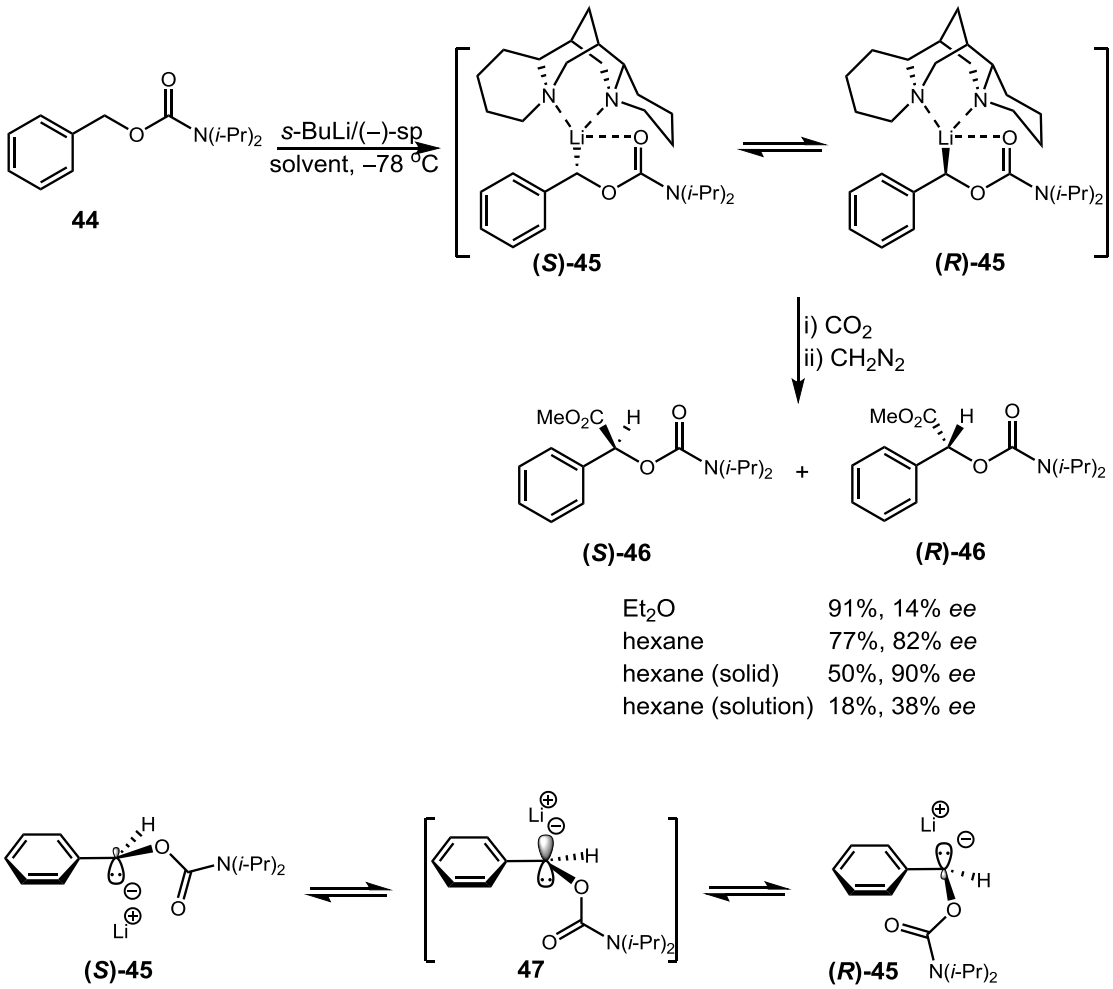
In addition to lithiated allyl carbamates, the benzyllithium counterparts were also explored. It was found that benzyl *N*,*N*-dialkylcarbamates can be deprotonated with the same ease as the corresponding allyl compounds. Hoppe and coworkers synthesised primary carbamates **38-40** and investigated their properties.[26] Benzyl esters **38-40** can be deprotonated by *n*-BuLi in the presence of TMEDA, generating the corresponding carbenoid, which further react with various kinds of electrophiles (*E*-X) and afford the α-substituted benzyl carbamates **41-43** generally in high yields (Scheme 1.8).




**38**: $R^1$ = H, $R^2$ = Me
**39**: $R^1$ = H, $R^2$ = Et
**40**: $R^1$ = OMe, $R^2$ = *i*-Pr

**41**: $R^1$ = H, $R^2$ = Me
**42**: $R^1$ = H, $R^2$ = Et
**43**: $R^1$ = OMe, $R^2$ = *i*-Pr

**Scheme 1.8.** Electrophilic substitutions of primary benzylic-type carbamates.



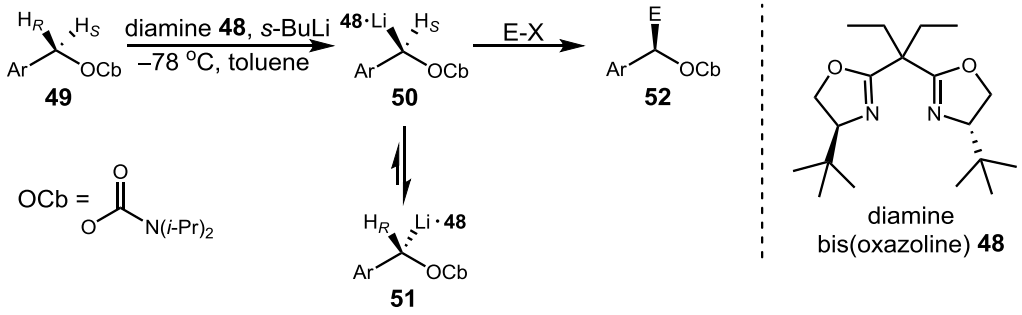

**Scheme 1.9.** Investigation of the stability of primary benzylic-type carbamate.

The configurational stability of lithiated primary carbamates were also explored.[27] Benzyl *N*,*N*-diisopropylcarbamate **44** was deprotonated by *s*-BuLi/(–)-sparteine in $Et_2O$ at cryogenic temperature (–78 °C). After 4 hours, the reaction was trapped by introduction of carbon dioxide, which was followed by esterification with diazomethane. The mandelic acid derivatives **(*S*)-46** and **(*R*)-46** were isolated with merely 14% *ee* in favour of **(*S*)-46** (Scheme 1.9). Utility of hexane in place of $Et_2O$ resulted in crystallisation of lithium carbamate **45** leading to the formation of **(*S*)-46** with 82% *ee*. In an additional experiment, the solution was isolated from the crystalline mass, and the two phases were manipulated separately; the enantioselectivity amounted to 38% and 90% *ee*, respectively (Scheme 1.9). It can be reasoned that lithium carbamates are configurationally labile in solution even at cryogenic temperature, and **(*S*)-46** undergoes racemisation via a planar configured carbanion **47** (Scheme 1.9) with lithium cation migration from one enantiotopic face to the other. As a result, the chiral

information of the enantioenriched carbenoid is significantly reduced and eventually **(*S*)-46** and **(*R*)-46** equilibrate even at low temperature.[27]

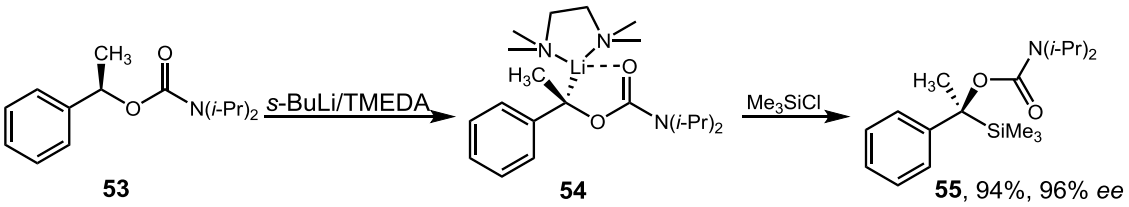
To overcome the configurational lability of lithiated primary benzyl carbamates, Hoppe and coworkers developed a methodology to improve the enantioenriched electrophilic substitution reaction using a chiral diamine ligand in the presence of *s*-BuLi.[28] The utility of chiral bis(oxazoline) ligand **48** afforded the optimal results. The investigation showed that, in contrast to the instance using (–)-sparteine, enantiotopic differentiation by bis(oxazoline) ligand **48** was poor and both diastereoisomers were generated. The epimeric complex-ion pairs reached equilibration generating one diastereoisomer nearly exclusively with reaction time extension. This can be owed to the thermodynamic resolution occurring after the deprotonation step, which eventually led to high enantioselectivity. The preferentially generated diastereoisomer was further reacted with a variety of electrophiles to yield α-substituted benzylic carbamates with high stereoselection.[28]

**Table 1.2.** Lithiation of primary benzyl carbamates using ligand **48**.



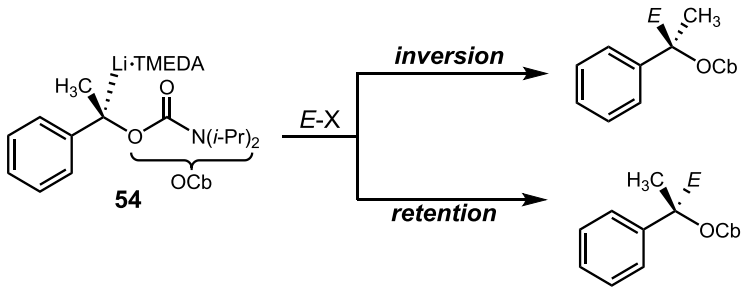

| E-X | Yield (%) | *ee* (%) | Product Configuration |
|---|---|---|---|
| $Bu_3SnCl$ | 88 | 98 | *R* |
| $Me_3SiCl$ | 98 | 98 | *R* |
| MeI | 98 | 96 | *R* |
| $CO_2$ | 99 | 95 | *S* |

Whereas the lithium derivatives of chiral primary benzyl carbamates are configurationally labile at –78 °C, it is not true in the case of lithiated secondary benzyl carbamates. The presence of an α-substituted alkyl group increases the stability of the generated carbanion, thus preventing the lithium cation migrating from one face of the carbanion to the other. As a consequence, intermediate **54** is configurationally stable at –78 °C.[29] Quaternary carbon centres can be formed with high enantioselectivity via the electrophilic substitution with electrophiles (Scheme 1.10).[29]




**Scheme 1.10.** Deprotonation of enantioenriched secondary benzyl carbamate.

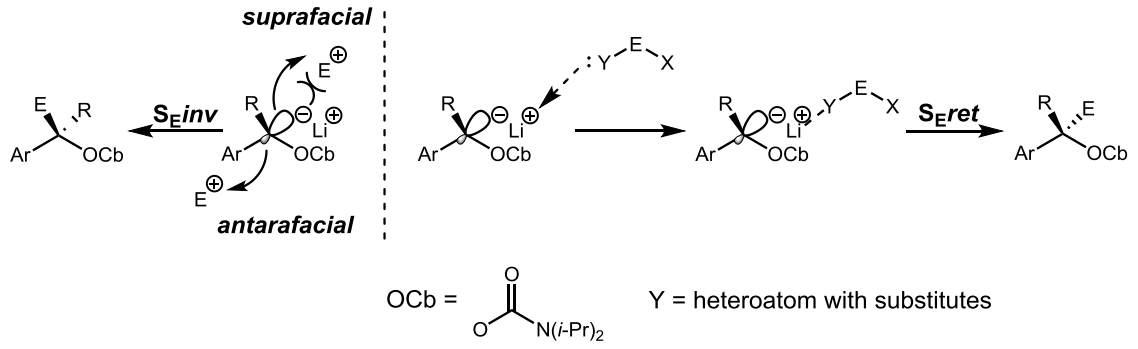
**Table 1.3.** Hoppe's homoaldol reaction with 2-alkenyl diisopropylcarbamate.




| E-X | Stereocontrol | Yield (%) | *ee* (%) |
|---|---|---|---|
| $(CH_3)_3SnCl$ | inversion | 92 | >95 |
| $CH_3OC(O)Cl$ | inversion | 90 | 85 |
| $CH_3OC(O)CN$ | inversion | 43 | 92 |
| $(CH_3)_3SiCl$ | retention | 94 | 96 |
| $CH_3OC(O)\ CH_3$ | retention | 85 | 94 |
| $HC(O)\ CH_3$ | retention | 60 | >95 |
| $PhC(O)\ CH_3$ | retention | 95 | >95 |

The lithiated secondary carbamates undergo electrophile-dependent stereodivergent substitution with either stereoretention or stereoinversion (Table 1.3).[29]

With respect to the stereoselection, a possible reason could lie in the inherent nature of the lithiated carbamate **54** (Scheme 1.11). The non-mesomerically stabilised benzyllithium derivative, with $sp^3$-hybridised carbon centre, has a flattened (but not completely planar) carbanionic moiety. Thus, there is considerable electron density at the rear face. The electrophiles can approach the central carbon antarafacially, avoiding steric congestion with lithium cation. Alternatively, when a favourable interaction with lithium cation can be accessible, a suprafacial attack will take place. Electrophiles, which possess an energetically low LUMO, but without good complexing groups for lithium cation (e.g. acid chlorides, cyanides, stannyl chlorides), prefer antarafacial attack; while electrophiles with an energetically higher LUMO and good electron-donating groups (such as alcohols, aldehydes, ketones, esters, alkyl halides) capable of coordinating to lithium cation would preferentially undergo a suprafacial attack (Scheme 1.11).




**Scheme 1.11.** Proposed mechanism for the stereoselection reactivity.

### 1.2.2. Hoppe-type Oxazolidine Carbamates

In addition to diisopropylcarbamate (Cb), another two types of carbamates, oxazolidine carbamates (Cby, Cbx), were also developed by Hoppe and coworkers (Figure 1.2). The oxazolidine carbamates can be easily removed by an acid/base hydrolysis using methanesulfonic acid and methanol followed by treatment with barium hydroxide.[30]

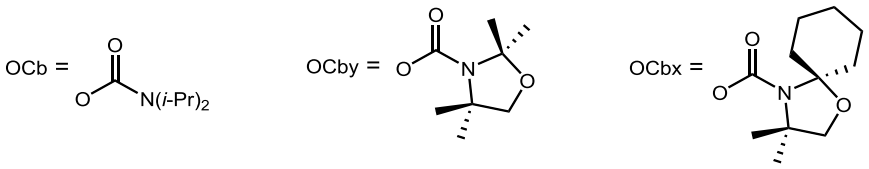
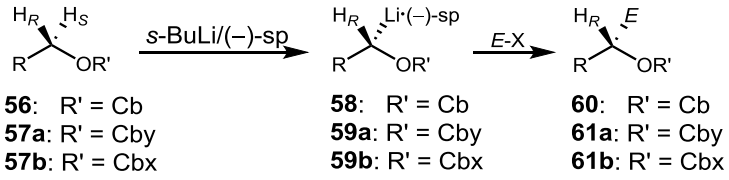



**Figure 1.2.** Carbamate groups developed by Hoppe and coworkers.

**Table 1.4.** Example of deprotonation and substitution of alkyl carbamates.




**56**: R' = Cb
**57a**: R' = Cby
**57b**: R' = Cbx

**58**: R' = Cb
**59a**: R' = Cby
**59b**: R' = Cbx

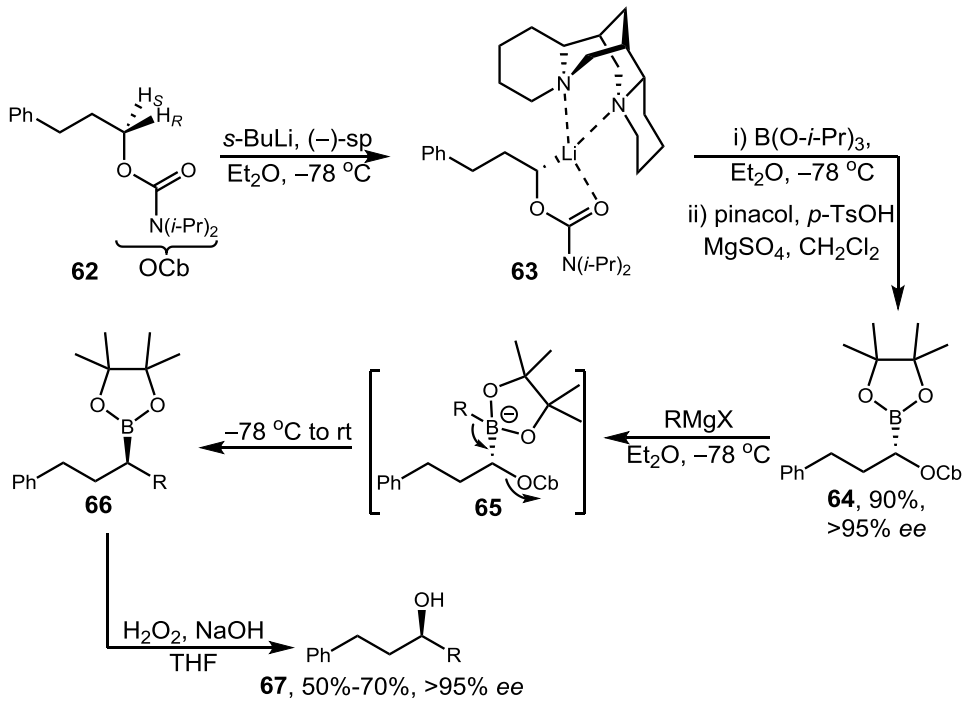
**60**: R' = Cb
**61a**: R' = Cby
**61b**: R' = Cbx

| R | Diamine | R' | E-X | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|
| $PhCH_2CH_2$ | (–)-sparteine | Cb | $Bu_3SnCl$ | 73 | 98 |
| $CH_3$ | (–)-sparteine | Cby | $(CH_3)_3SnCl$ | 73 | >95 |
| $CH_3$ | (–)-sparteine | Cbx | $(CH_3)_3SnCl$ | 76 | >95 |
| $CH_3$ | (–)-sparteine | Cby | $CO_2$ | 75 | >95 |
| $CH_3$ | (–)-sparteine | Cbx | $ClCO_2CH_3$ | 73 | >95 |
| $CH_3(CH_2)_6$ | (–)-sparteine | Cby | $CH_3I$ | 87 | >95 |
| $CH_3(CH_2)_5$ | (–)-sparteine | Cbx | $CH_3I$ | 81 | 96 |
| $CH_3$ | (–)-sparteine | Cby | $(CH_3)_3SiCl$ | 86 | >95 |
| $CH_3$ | TMEDA | Cbx | $(CH_3)_3SiCl$ | 70 | -- |

The treatment of alkyl carbamates of types **56** or **57** with *s*-BuLi and (–)-sparteine normally proceeds in $Et_2O$ or a hydrocarbon with a preferential removal of the *pro-S*-proton to give the lithium derivative **58** or **59**, which can further react with various electrophiles to yield α-substituted carbamates **60** or **61**, respectively, in good yield and with excellent stereoselection (Table 1.4). Reactions using TMEDA instead of (–)-sparteine also proceed well affording racemic product (Table 1.4).[31]

### 1.2.3. Hoppe's Exploration into Lithiation–Borylation

In addition to substitution reactions with the aforementioned electrophiles, Hoppe and coworkers also investigated the reactions of lithiated carbamates with organoboron compounds.[32] The lithiated carbamate **63** was treated with triisopropyl borate, which was followed by an acidic workup and transesterification with pinacol leading to enantioenriched boronic ester **64**. Treatment of ester **64** with Grignard reagents generated the intermediate boronate complex **65**, which afforded desired product **66** via 1,2-metalate rearrangement, upon warming to ambient temperature, with R group migration with configurational inversion at the chiral centre. The subsequent oxidation of boronic ester **66** resulted in the formation of corresponding secondary chiral alcohol **67** in good yield and with excellent stereoselectivity (Scheme 1.12).[32]



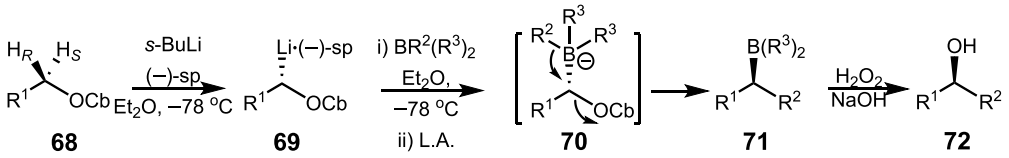

**Scheme 1.12.** Hoppe-type 1,2-metalate rearrangement from chiral secondary boronic ester.

## *1.3. Lithiation–Borylation with Hoppe-type Carbenoids*

### 1.3.1. Lithiation–Borylation with Primary Carbamates and Benzoates

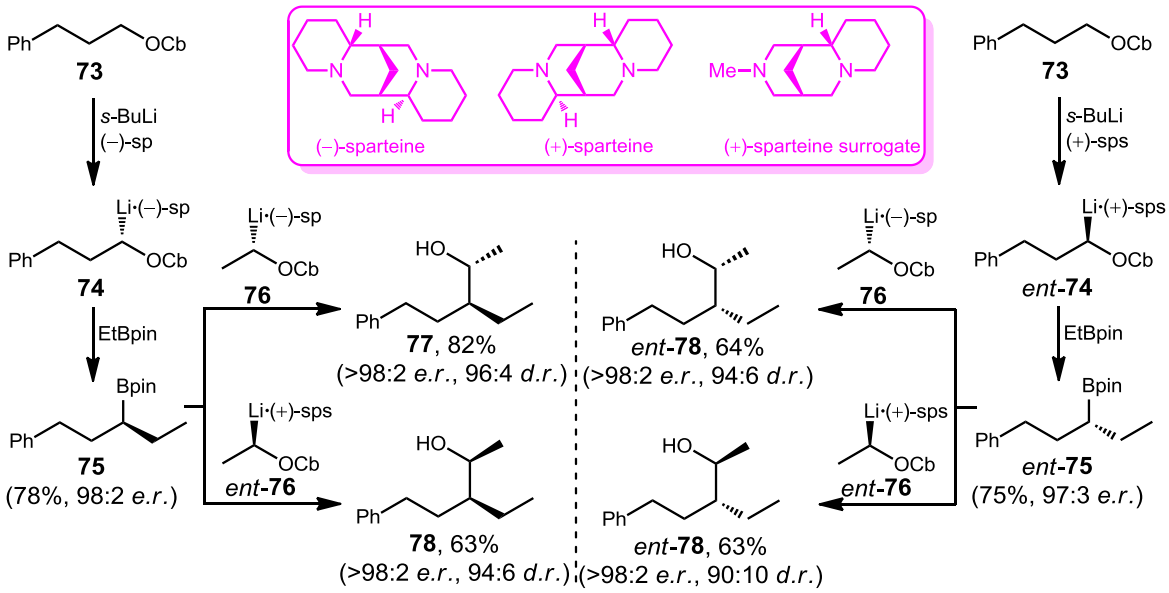
In spite of the initial positive results, Hoppe and coworkers did not investigate the direct reaction of lithiated carbamates with organic boranes or boronates. In 2007, Aggarwal and coworkers reported the direct reaction of lithiated carbamates with organoborons (boranes and boronic esters), furnishing the corresponding homologated organoborons in high yields and excellent enantioselectivity.[33] As described in Table 1.5, the configurationally stable organolithium **69**, generated from asymmetric deprotonation of carbamate **68**, immediately reacted with various organoborons and generated the boronate complex **70** with retention of configuration. Subsequent stereospecific 1,2-metalate rearrangement and *in situ* oxidation furnished the homologated secondary alcohols **72**.[33]

**Table 1.5.** Lithiation–Borylation reactions with primary Hoppe-type carbamates.




| $R^1$ | $R^2$ | $(R_3)_2$ | Lewis acid | Yield (%) | er |
|---|---|---|---|---|---|
| $Ph(CH_2)_2$ | Et | Et | -- | 91 | 98:2 |
| $Ph(CH_2)_2$ | *n*-hex | 9-BBN | -- | 90 | 98:2 |
| $Ph(CH_2)_2$ | *i*-Pr | 9-BBN | -- | 81 | 98:2 |
| $Me_2C{=}CH(CH_2)_2$ | Et | Et | -- | 90 | 97:3 |
| $TBSO(CH_2)_2C(Me)_2CH_2$ | Et | Et | -- | 67 | 95:5 |
| $Ph(CH_2)_2$ | Ph | 9-BBN | $MgBr_2$ | 94 | 97:3 |
| $Ph(CH_2)_2$ | Et | pinacol | $MgBr_2$ | 90 | 98:2 |
| $Me_2C{=}CH(CH_2)_2$ | Et | pinacol | $MgBr_2$ | 75 | 97:3 |
| $TBSO(CH_2)_2C(Me)_2CH_2$ | Ph | pinacol | $MgBr_2$ | 64 | 98:2 |
| *i*-Pr | Ph | pinacol | $MgBr_2$ | 70 | 98:2 |
| Me | Ph | pinacol | $MgBr_2$ | 70 | 97:3 |

The reaction proved to be very effective with a variety of aryl and alkyl substituted boranes and boronic esters (Table 1.5). Generally, the 1,2-metalate rearrangement is considerably faster with boranes than with boronic esters starting to occur at –40 °C; whereas in the cases of boronic esters, high temperatures (refluxing $Et_2O$) and Lewis acidic $MgBr_2$ were required to promote the 1,2-migration process. Phenyl group was also found to be a slow migrating group requiring the use of Lewis acid at reflux.

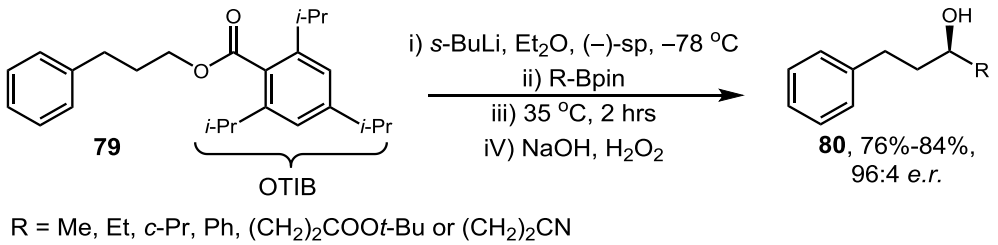



**Scheme 1.13.** Iterative homologation of boronic esters **75** and *ent*-**75**.

Additionally, Aggarwal and coworkers demonstrated this methodology can be applied in an iterative manner, and they accomplished the stereocontrolled synthesis of scaffolds bearing multiple adjacent stereogenic centres.[33] The homologation process was initiated by the lithiation of carbamate **73** with addition of (–)-sparteine, generating the lithiated carbamate **74**. The subsequent addition of boronic ester EtBpin trapped **74** and gave homologated boronic ester **75** in 78% yield and 98:2 *e.r.* upon warming to ambient temperature (Scheme 1.13). The reaction of boronic ester **75** with organolithium **76** afforded, after *in situ* oxidation, the desired alcohol **77** as a mixture of diastereoisomers with >98:2 *e.r.* The other diastereomer **78** is potentially accessible by using the opposite enantiomer of the lithiated carbamate, *ent*-**76**. When O'Brien's enantiomeric (+)-sparteine surrogate, derived from (–)-cytisine, was used to generate *ent*-**76**, the alternative diastereomer **78** was furnished with comparably high diastereoselectivity (94:6 *d.r.*) and enantioselectivity (*e.r.* > 98:2; Scheme 1.13). The enantiomeric pair to

**77** and **78** was readily accessed with similarly excellent *d.r.* and *e.r.* by utilising the same protocol but starting from *ent*-**75**, which was generated from the first homologation employing (+)-sparteine surrogate (Scheme 1.13).[33]

In 2011, Aggarwal and coworkers addressed the slow migration problem of certain boronic esters by employing alkyl 2,4,6-triisopropylbenzoates in place of the corresponding carbamates.[34] It was discovered that the benzoate demonstrated similar behaviours to the corresponding carbamates in asymmetric deprotonation, albeit with slightly lower *e.r.* (96:4), but can result in substantially faster 1,2-metalate rearrangement, allowing even the most reluctant of migrating groups (e.g. Me, $(CH_2)_2CN$) to engage in the reaction, without the need for Lewis acid additive.[34] Using the benzoate esters, a diverse array of homologated secondary alcohols can be delivered in good yield and excellent stereoselectivity (Scheme 1.14).




**Scheme 1.14.** Lithiation–Borylation with 2,4,6-triisopropylbenzoate.

To showcase the power of lithiation–borylation, Aggarwal and coworkers applied the methodology in a variety of natural product synthesis. Figure 1.3 summarised a variety of natural products that were successfully synthesised utilising homologation of boronic esters employing lithiated primary carbamate.[35-42] The total synthesis of insect pheromone (+)-faranal **81**[35] and virulence factor mycolactone **88**[42] are representative.

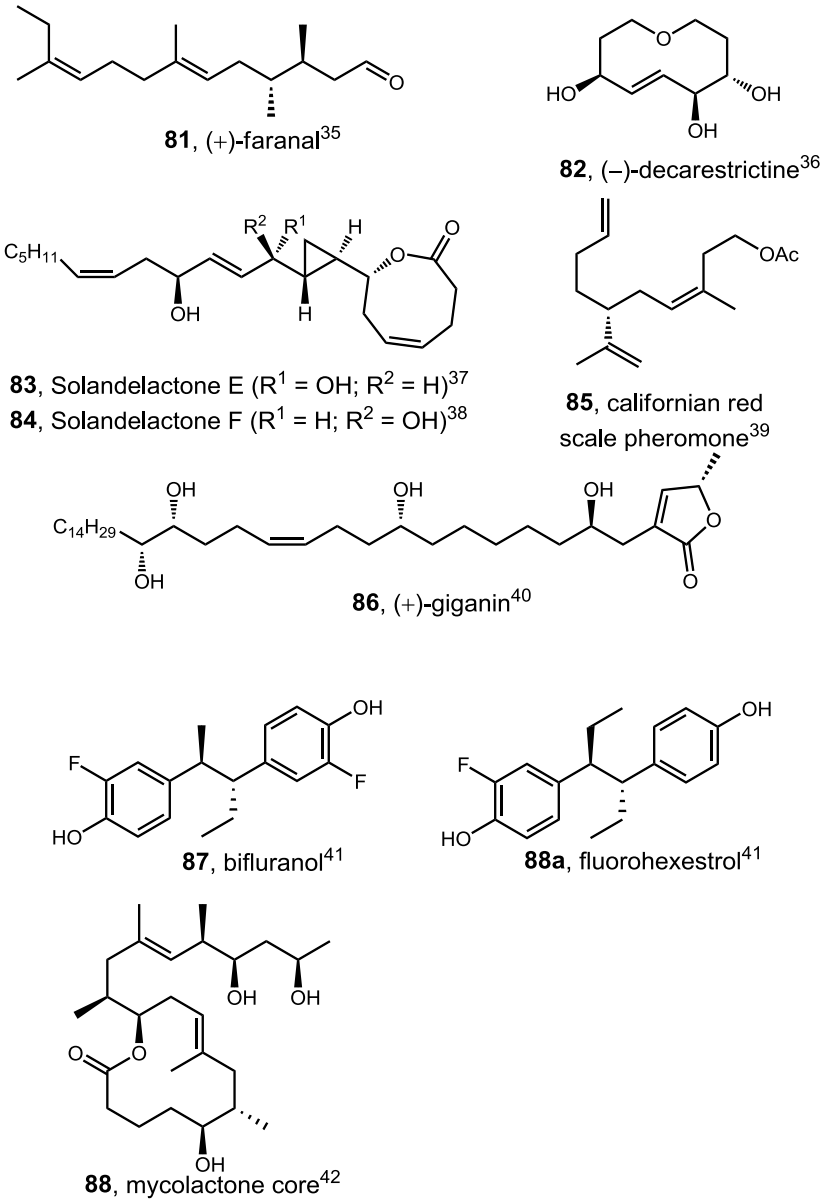
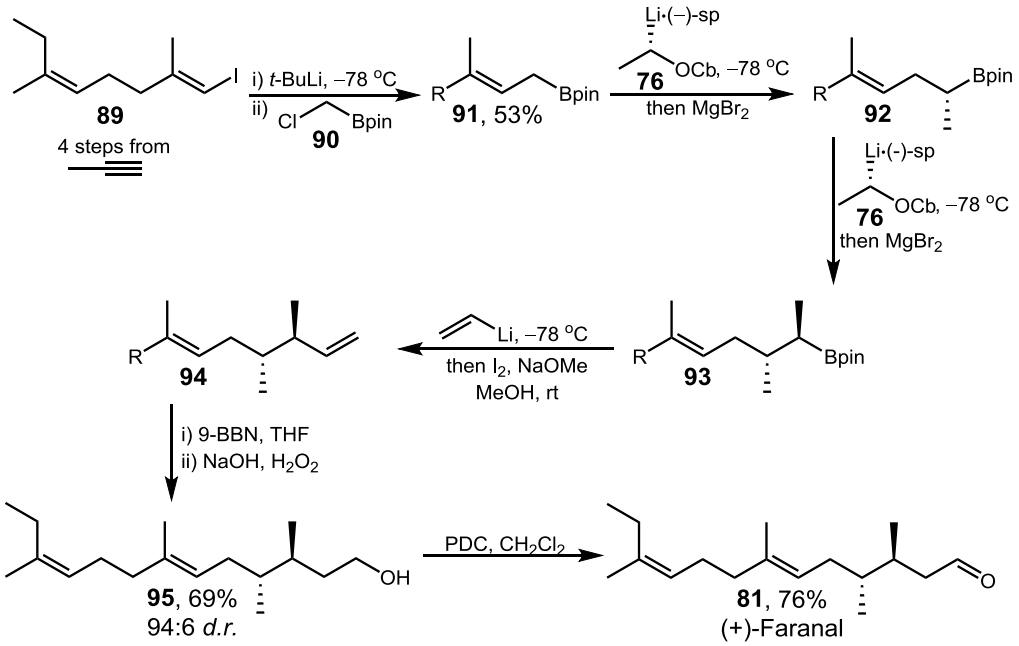



**Figure 1.3** The applications of lithiation–borylation in natural products.

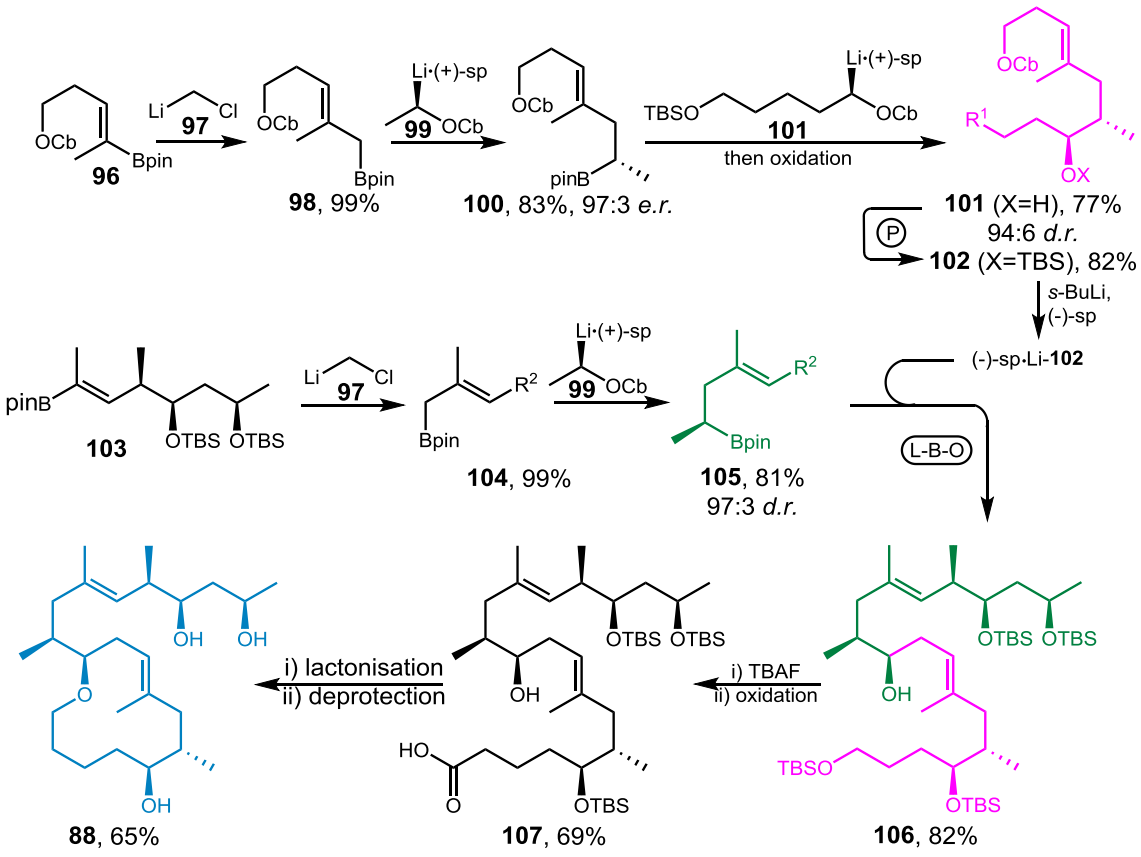
The synthesis of (+)-faranal **81**[35] started with the preparation of vinyl iodide **89**, which was synthesised in four steps from propyne (Scheme 1.15). Subsequently, the addition of *tert*-BuLi to vinyl iodide **89** triggered a lithium-iodide exchange. The generated organolithium was trapped by addition of chloromethyl boronate **90** and gave allylic boronic ester **91** in 53% yield. Two subsequent iterative lithiation–borylation reactions employing chiral organolithium **76** afforded homologated boronic ester **93**, which further underwent, without purification, Zweifel olefination, hydroboration and oxidation to furnish alcohol **95** in 69% yield and 94:6 *d.r.* It is noteworthy that vinyl iodide **89** can be converted into alcohol **95** in 40% yield by carrying out all four

homologations in a one-pot process, without purification of any of the intermediates, which can simplify the experimental operations without detriment to the selectivity (94:6 *d.r.*). The final product, (+)-faranal **81**, can be delivered by oxidation using PDC in 76% yield.[35]




**Scheme 1.15.** Total synthesis of (+)-faranal **81**.[35]

The mycolactone core **88** was also effectively synthesised utilising the lithiation–borylation strategy (Scheme 1.16).[42] The key step is the lithiation–borylation reaction of carbamate **102** and boronic ester **105**. The synthesis of fragment **102** started from the Matteson homologation of boronic ester **96** and chloromethyl lithium **97**, affording boronic ester **98** in 99% yield, which underwent another two lithiation–borylation reactions with lithiated carbamates **99** and **101** respectively, to furnish, after subsequent oxidation, carbamate **101** in 63% overall yield and excellent stereoselectivity. Remarkably, it was also found that the whole homologation process can be performed sequentially, without intermediate purification (one-pot way), with the yield increased to 81% and equally high *d.r.* Further protection of **101** gave compound **102** in 82% yield (Scheme 1.16). For the preparation of fragment **105**, boronic ester **103** was subjected to Matteson homologation and lithiation–borylation sequentially, and the desired product was formed in good yield and excellent *d.r.*




**Scheme 1.16.** Total synthesis of (+)-mycolactone core **88**.

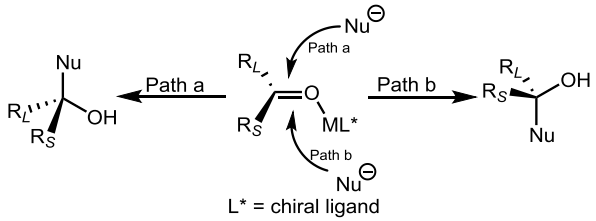
With the two key fragments in hand, the final lithiation–borylation was examined. Treatment of carbamate **102** with *s*-BuLi and (–)-sparteine led to the formation of corresponding lithiated carbamate, which was trapped with electrophilic boronic ester **105** and afforded, with subsequent oxidation, alcohol **106** in 82% yield and high *d.r.* Once again, the direct transformation of boronic ester **103** to alcohol **106** can conducted in a one-pot way with an increase in yield (from 66% to 86%) and same selectivity. Alcohol **106** further underwent oxidation, lactonisation and deprotection, furnishing the final target product **88** (Scheme 1.16).[42]

### 1.3.2. Lithiation–Borylation with Secondary Carbamates and Benzoates

Aggarwal and coworkers further explored the application of lithiation–borylation in the synthesis of enantioenriched tertiary alcohols.[43] Whilst the enantioselective synthesis of

secondary alcohols has been extensively explored over the past decades,[44-45] the chiral synthesis of compounds with quaternary stereogenic centres still remains challenging.[46-48]

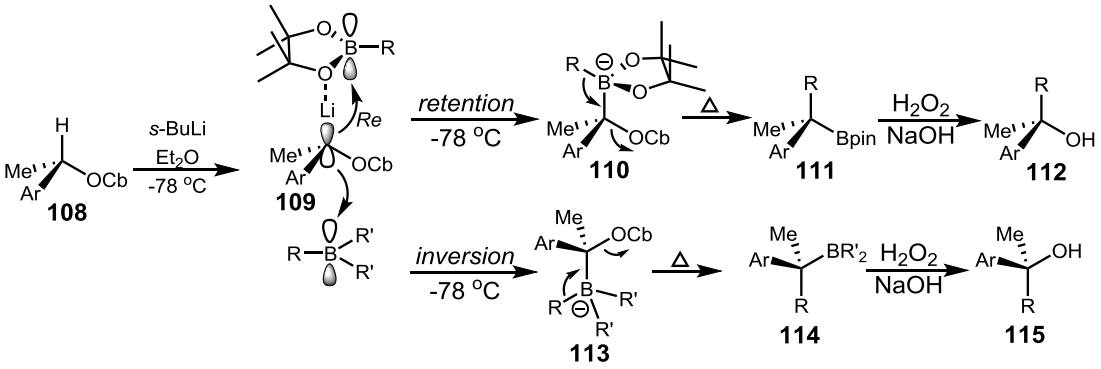
Tertiary alcohols normally can be prepared via the addition reaction of organometallic reagents and ketones. Although some asymmetric additions using chiral ligands were developed,[49-51] the stereoselectivity can be low since the process relies on the steric differences between the carbonyl substituents.




**Scheme 1.17.** Synthesis of tertiary alcohols via addition of organometallic reagents to ketones.

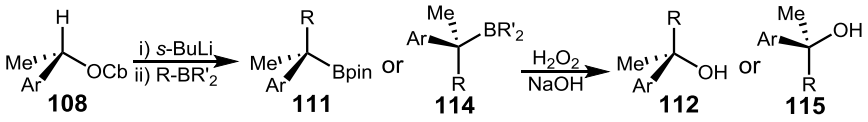
The lithiation–borylation reaction can be utilised in the stereocontrolled synthesis of tertiary alcohols. As discussed in §1.2.1, lithiated primary benzyl carbamates generated by kinetic deprotonation are configurationally unstable even at very low temperatures, which can be overcome by use of bis(oxazoline) ligands under thermodynamic control.[52] On the contrary, lithiated secondary benzyl carbamates are comparably configurationally stable at cryogenic temperature providing the possibility of application in lithiation–borylation reactions.[29,53] Aggarwal and coworkers successfully developed the lithiation–borylation methodology employing secondary benzylic carbamates.[43] The desired tertiary alcohols were generated with high levels of enantiospecificity using the lithiation–borylation of secondary boronic esters. Both boranes and a wide array of boronic esters were effective in this reaction. It is noteworthy that, different from primary carbamates reacting with stereoretention with both boranes and boronic esters, secondary benzylic carbamates react with retention with boronic esters but inversion with boranes.[43a,54] The origin of difference in selectivity can be rationalised by the proposed model in Scheme 1.18. In the cases of boronic esters, the oxygen atom of boronic esters can complex the lithium atom of lithiated carbamates and be delivered on the same face as the metal. Whilst in the cases of boranes, the addition can take place on the opposite face to the metal in the absence

of complexation between the pinacol oxygen atom and lithium cation, where there is significantly high electron density due to the mesometric stabilisation, resulting in the inversion of configuration (Scheme 1.18). The successful development of this methodology allows for the synthesis of both enantiomers of asymmetric tertiary alcohols from the corresponding secondary alcohols, which can be synthesised using Noyori transfer hydrogenation[55] with an *e.r.* of up to 99:1.




**Scheme 1.18.** Lithiation–borylation of secondary benzylic carbamates.

**Table 1.6.** Lithiation–Borylation reactions with secondary benzylic carbamates.

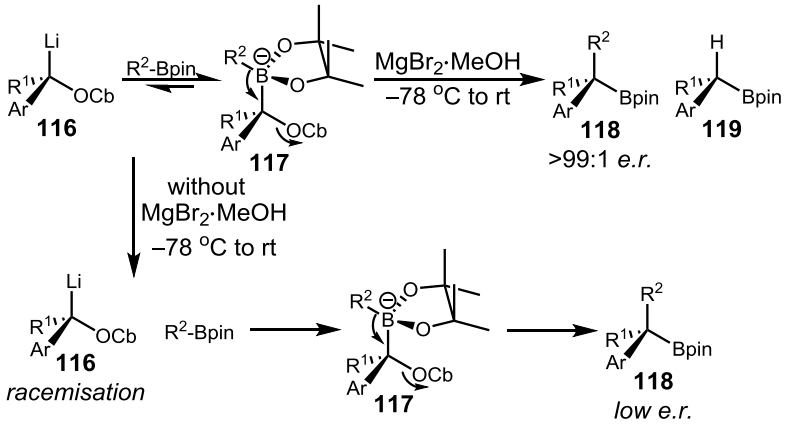



| Ar | R | R'$_2$ | Yield (%) | er (*S*/*R*) |
|---|---|---|---|---|
| Ph | Et | $Et_2$ | 91 | 99:1 |
| Ph | Et | Pinacol | 95 | 1:99 |
| Ph | vinyl | Pinacol | 75 | 2:98 |
| Ph | *p*-Cl-$C_6H_4$ | Pinacol | 92 | 99:1 |
| *p*-Cl-$C_6H_4$ | Et | Pinacol | 92 | 4:96 |
| *p*-MeO-$C_6H_4$ | Et | Pinacol | 97 | 2:98 |

The substrate scope was extensively explored with a wide range of alkyl, vinyl, allyl, aryl and heterocyclic boronic esters and various types of secondary alcohols containing

both electron-rich and electron-deficient aromatics, achieving excellent enantioselectivity in all cases (Table 1.6).[43a]

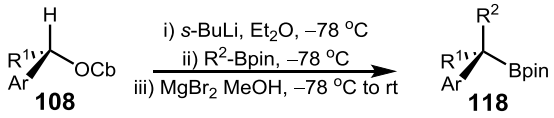
For especially steric hindered boronic ester or carbamates bearing electron-withdrawing substituents on the aromatic rings, some erosion in *ee* occurred during the lithiation–borylation process.[43b] A possible explanation for this erosion was described in Scheme 1.19. It is proposed that formation of boronate complex **117** is reversible. The boronate complex can undergo dissociation back to starting boronic ester and lithiated carbamate **116** species. Racemisation of regenerated lithiated carbamate **116** can take place upon warming, before recombination with the boronic ester, thereby leading to erosion in enantiomeric excess of the homologated boronic ester.




**Scheme 1.19.** Proposed cause of erosion in enantioselectivity.

The problem was found to be resolved by addition of a second, more reactive electrophile than boronic ester after boronate complex formation. The presence of additive can quench any lithiated carbamate **116** generated from the reverse reaction, which would prevent the recombination of racemised lithiated carbamate **116** with boronic ester, thus preventing erosion of enantioselectivity. After carefully exploring different electrophiles, MeOH was proved to be an effective option and is normally used in combination with $MgBr_2$, which would both quench the reformed lithiated carbamate and accelerate the 1,2-metalate rearrangement. A broad range of secondary carbamates and various sterically congested boronic esters were explored under these conditions, affording the desired products in high yields and excellent enantioselectivity (Table 1.7).[43b]

**Table 1.7.** Lithiation–Borylation reactions of secondary benzylic carbamates with MeOH·$MgBr_2$.




| Ar | $R^1$ | $R^2$ | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| Ph | Me | *c*-Hex | 87 | 99 |
| Ph | Et | *i*-Pr | 74 | 99 |
| 4-Cl-$C_6H_4$ | Me | Et | 91 | 99 |
| 4-F-$C_6H_4$ | Me | *i*-Pr | 88 | 99 |
| 2-Me-$C_6H_4$ | Me | Ph | 64 | 99 |
| 2-MeO-$C_6H_4$ | Me | *i*-Pr | 79 | 99 |

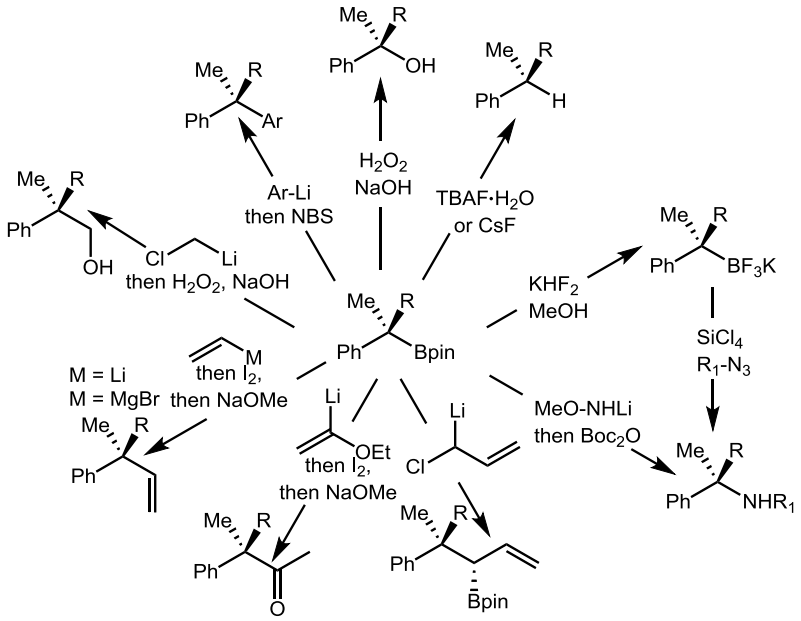
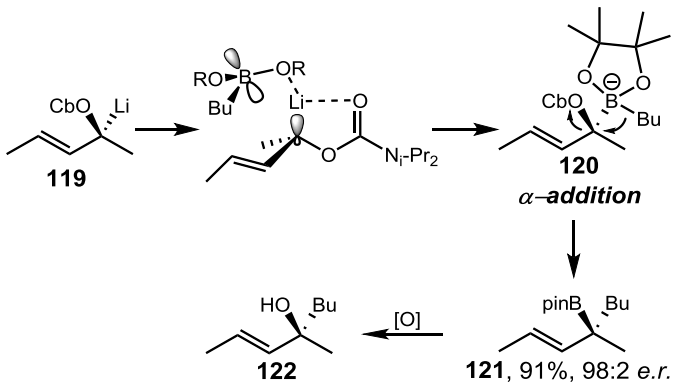



**Figure 1.4.** Functionalisation of tertiary boronic esters.

Tertiary boronic esters and boranes are a very versatile class of compounds that can subject to a broad range of stereospecific functionalisation (Figure 1.4), such as synthetically conductive oxidation, amination,[56] protodeboronation[57,58] and arylation.[59] In addition, applications in a variety of carbon-based homologations can give access to

asymmetric quaternary centres (Figure 1.4).[60,61] All the applications demonstrate the powerful efficiency of lithiation–borylation reaction.

In addition to secondary benzylic carbamates, the secondary allylic carbamates were examined in lithiation–borylation reactions. Lithiated primary allylic carbamates are, like primary benzylic carbamates, configurationally labile, whereas lithiated secondary allylic carbamates show configurational stability. However, the reaction of lithiated secondary allylic carbamates and electrophiles normally produces mixtures of α- and γ-addition products.[62-64] In sharp contrast, Aggarwal and coworkers discovered that the lithiation–borylation reaction using secondary allylic carbamates demonstrated high regioselectivity with α-addition products, and excellent *e.r.* was obtained (Scheme 1.20).[65] The high selectivity observed by Aggarwal and coworkers can be rationalised on the basis of the precoordination of the oxygen of boronic ester to the metal of the lithiated carbamate, which will deliver the boron reagent at the same site and side as the metal, leading to both high regioselectivity and enantioselectivity (Scheme1.20).




**Scheme 1.20.** The lithiation–borylation of secondary allylic carbamates.

Aggarwal and coworkers subsequently applied this methodology in the synthesis of the natural product C30 botryoccocene **123**[65] and the universal mating hormone α-1 **124** (Figure 1.5).[66] To synthesise the latter natural product **124**, secondary carbamate **125** was subjected to lithiation–borylation with boronic ester **126** (synthesised in six steps from the corresponding Roche ester) in the presence of *s*-BuLi and TMEDA and afforded, after oxidation, the homologated product **127**. Carbamate **127** further underwent hydrogenation and protection to give carbamate **128**, which was subjected to

another lithiation–borylation–oxidation with boronic ester **129** (prepared in four steps), furnishing secondary alcohol **130**. Subsequent oxidation and deprotection delivered the target α-1 hormone **124** in 21% overall yield and 96:4 *d.r.* (Scheme 1.21).[66]

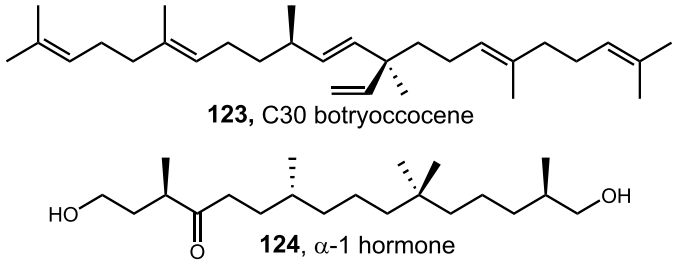
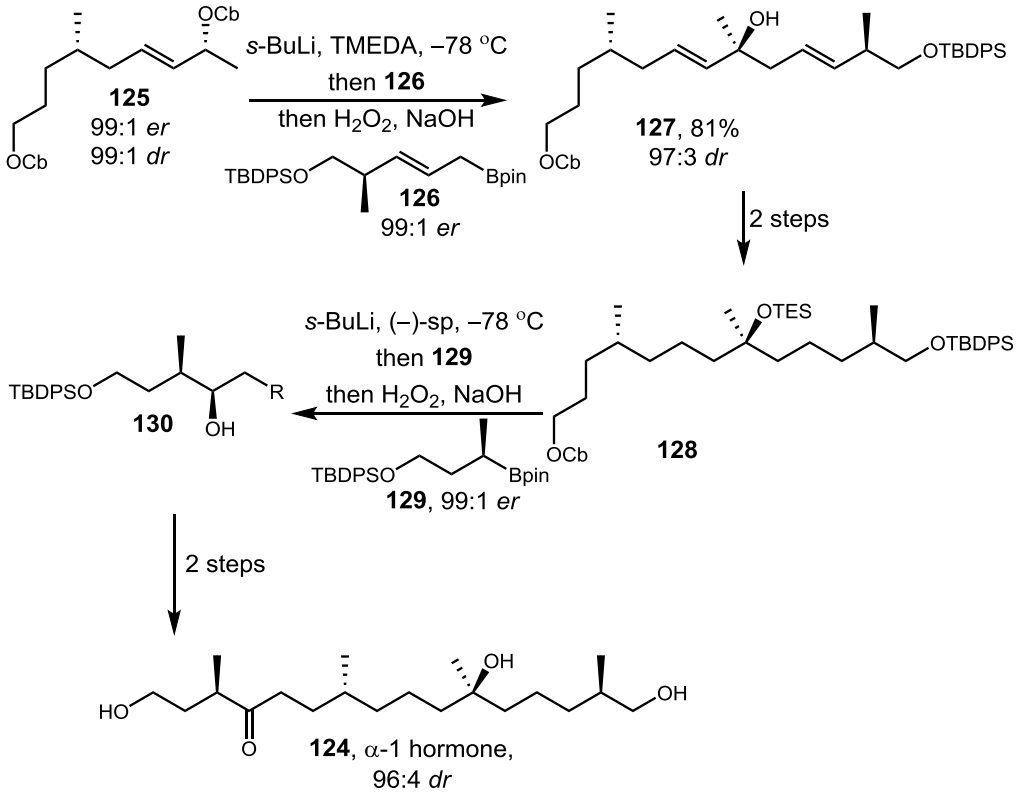


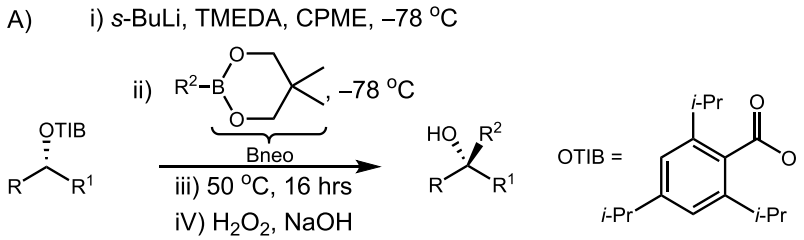

**Figure 1.5.** Synthetic applications using lithiation-borylation with secondary allylic carbamates.

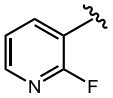


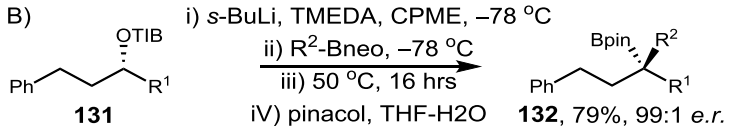

**Scheme 1.21.** Synthesis of natural product α-1 hormone **124**.

A limitation of employing secondary carbamates in lithiation−borylation reaction, is that the aryl or allyl group was required to provide an acidic proton at the benzylic or allylic position for the lithiation step. The deprotonation cannot occur without these groups.[67] Alternatively, secondary benzoate esters, without groups that acidify the

adjacent proton, were proved to be effective in lithiation–borylation reactions.[68] By employing alternative solvents and additives, Aggarwal and coworkers successfully identified conditions for the deprotonation of less acidic secondary benzoate esters (Scheme 1.22).[68] Subsequent addition of neopentyl boronic esters gave, after a 1,2-metalate rearrangement, the desired homologated boronic esters, which further underwent oxidation (Scheme 1.22A) or *in situ* transesterification with pinacol (to aid the purification and stability) in high yield and excellent *es* (Scheme 1.22B). The pinacol boronic esters can also be directly used in the reaction but the levels of *es* (~95%) were slightly decreased.



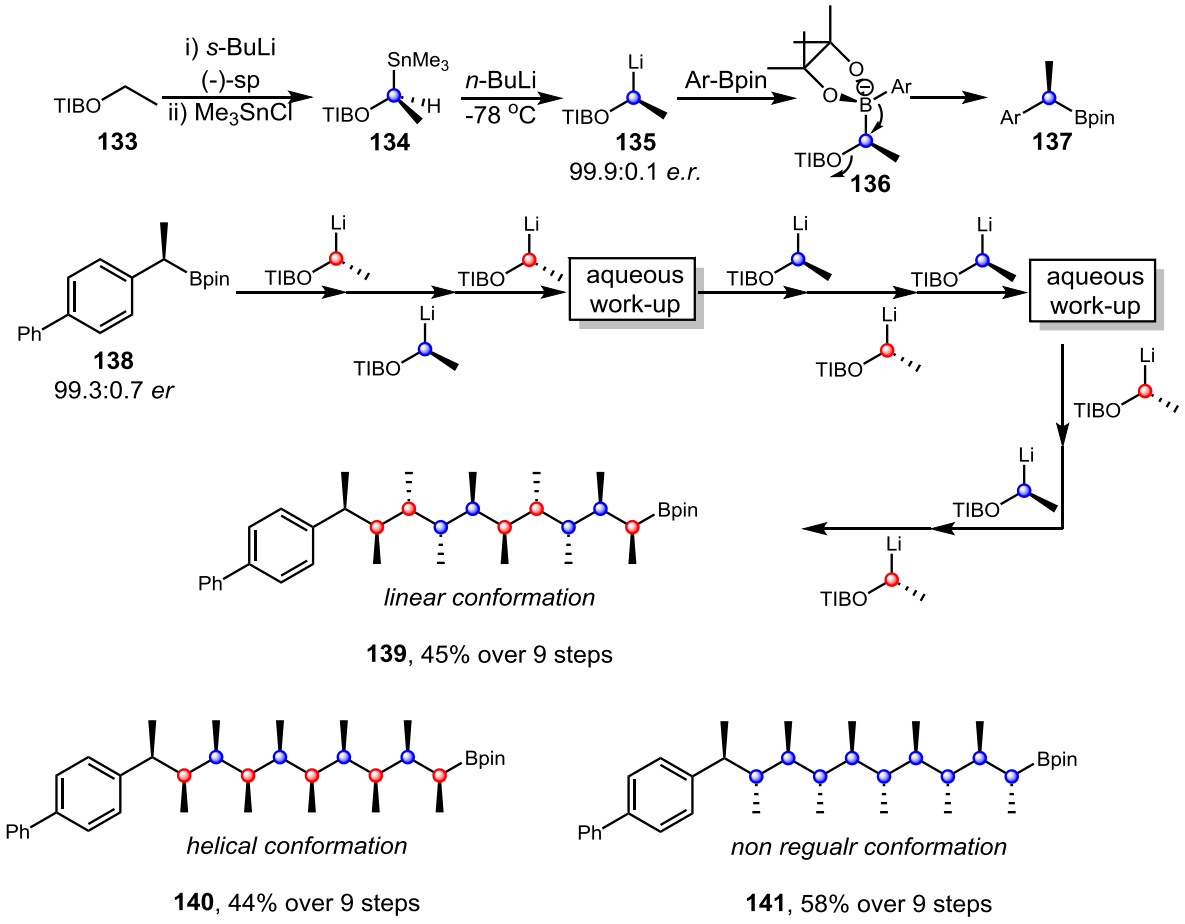

| R | $R^1$ | $R^2$ | Yield (%) | *er* |
|---|---|---|---|---|
| $Ph(CH_2)_2$ | Me | Et | 80 | 99:1 |
| $Ph(CH_2)_2$ | Me | $(CH_2)_2CO_2t$-Bu | 69 | 98:2 |
| $Ph(CH_2)_2$ | Me |  | 73 | 99:1 |
| $THPO(CH_2)_3$ | Me | Et | 72 | 99:1 |
| $Ph(CH_2)_2$ | Et | allyl | 40 | 99:1 |




**Scheme 1.22.** Lithiation–borylation reactions using secondary alkyl benzoates.

### 1.3.3. Assembly Line Synthesis

Recently, Aggarwal and coworkers have further demonstrated the high efficiency of iterative lithiation–borylation methodology by accomplishing the one-pot homologation of boronic esters to furnish long sequences with contiguous stereogenic centres. This strategy can be compared to a molecular assembly line where successive groups are added to a growing chain by reagent control strategy (Scheme 1.23).[69] Enantioenriched stannanes **134** and ***ent*-134** can be prepared by deprotonation in the presence of chiral base *s*-BuLi·(–)-sp or *s*-BuLi·(+)-sp, which were subsequently trapped with $Me_3SnCl$. After recrystallisation, **134** and ***ent*-134** were obtained with 99.9:0.1 *e.r.*, which was converted to the lithiated benzoate ester **135** by lithium-tin exchange with stereoretention at cryogenic temperature. The *in situ* generated organolithium was further reacted with aryl boronic ester, affording boronate complex **136**. The successive 1,2-metalate rearrangement of complex **136** gave, upon warming to elevated temperature, boronic ester **137**. The reaction mixture was filtered to remove insoluble lithium benzoate and subjected to subsequent homologations without purification. The process was repeated iteratively and a total of nine homologations were carried out. Aqueous workup, without further purification, was performed every three homologations. The iterative assembly line synthesis yielded the long carbon chain **139** bearing 10 continuous methyl substituents with full control of both absolute and relative stereochemistry. In addition, the alternating *syn-anti* isomer **141** and all *syn* isomer **142** were furnished by the appropriate selection of enantiomer of lithiated benzoate ester. It was discovered that isomer **139** adopted a linear conformation, while isomer **140** adopted a helical conformation; whilst the alternating *syn-anti* isomer **141** did not adopt a particular low energy conformation (Scheme 1.23).[69]







**Scheme 1.23.** Examples of assembly line synthesis.

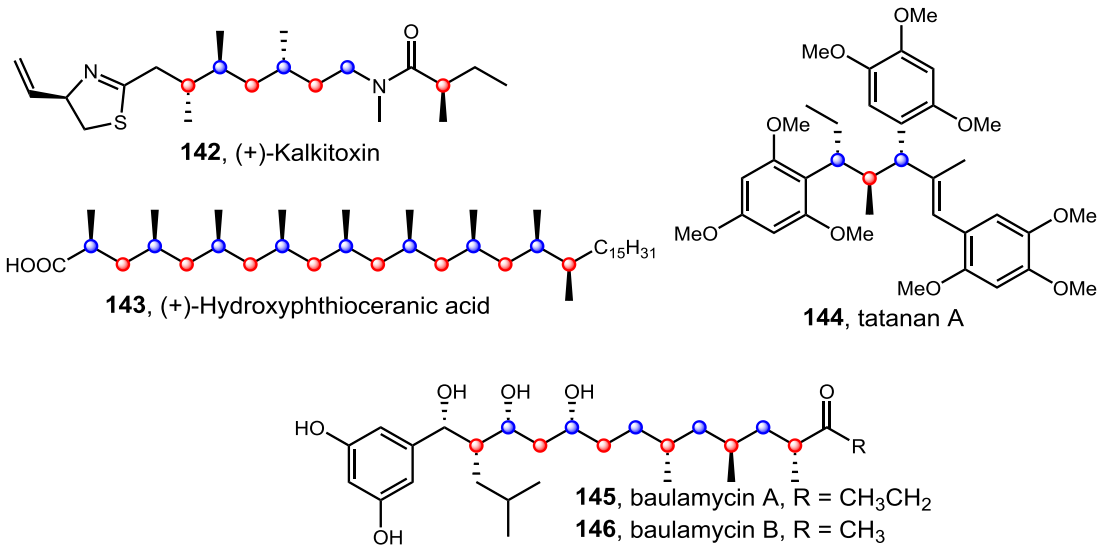



**Figure 1.6.** Synthetic applications of assembly line synthesis.

Successfully developing the assembly line synthesis, Aggarwal and coworkers applied this strategy to the synthesis of various natural products, such as (+)-kalkitoxin **142**,[70] (+)-hydroxyphthioceranic acid **143**,[70] tatanan A **144**[71] and baulamycin A **145**[72] and B **146**,[72] which demonstrate its high efficiency (Figure 1.6).

## *1.4. Transformations of Boronic Esters*

A broad range of reactions can be carried out using organic boronic esters, which lead to the transformation of the boron moiety into various kinds of functional groups (Figure 1.7). These conversions usually proceed in either a stereoretentive or a stereoinvertive manner, affording the anticipated products with high stereospecificity.

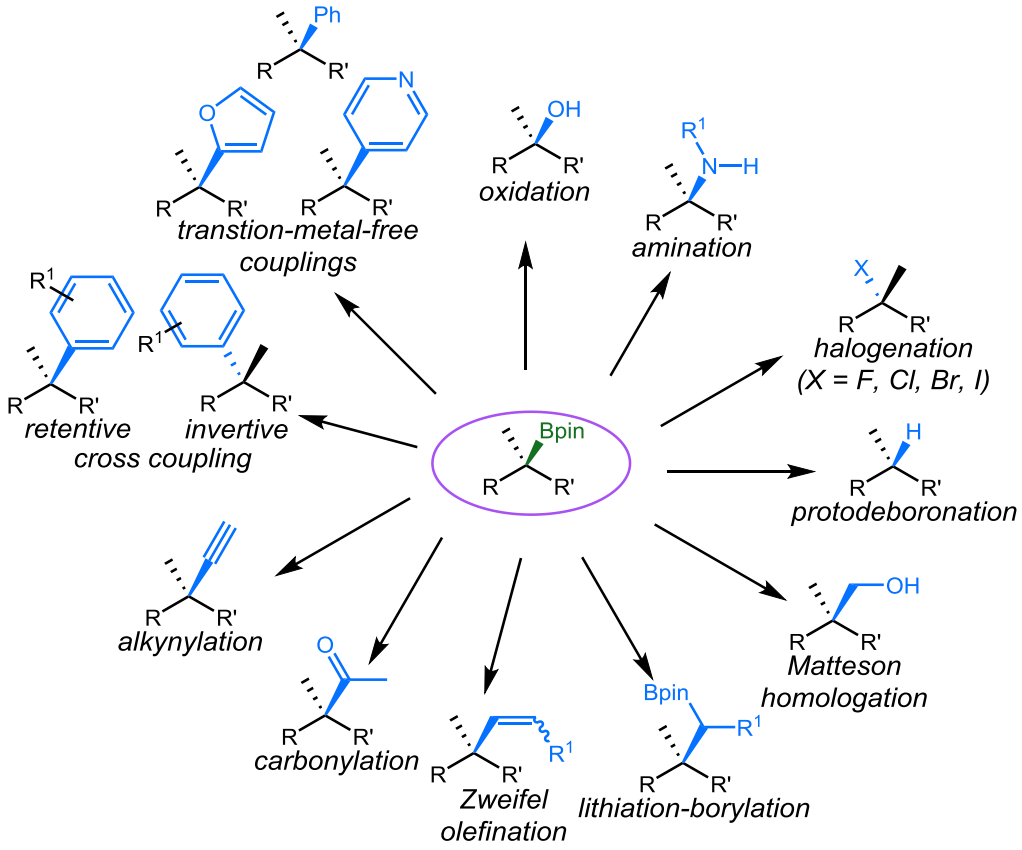
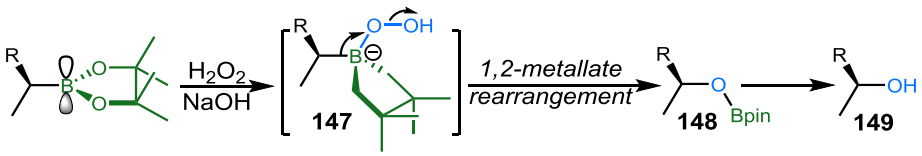



**Figure 1.7.** Summary of stereospecific functional group transformations of secondary and tertiary boronic esters.

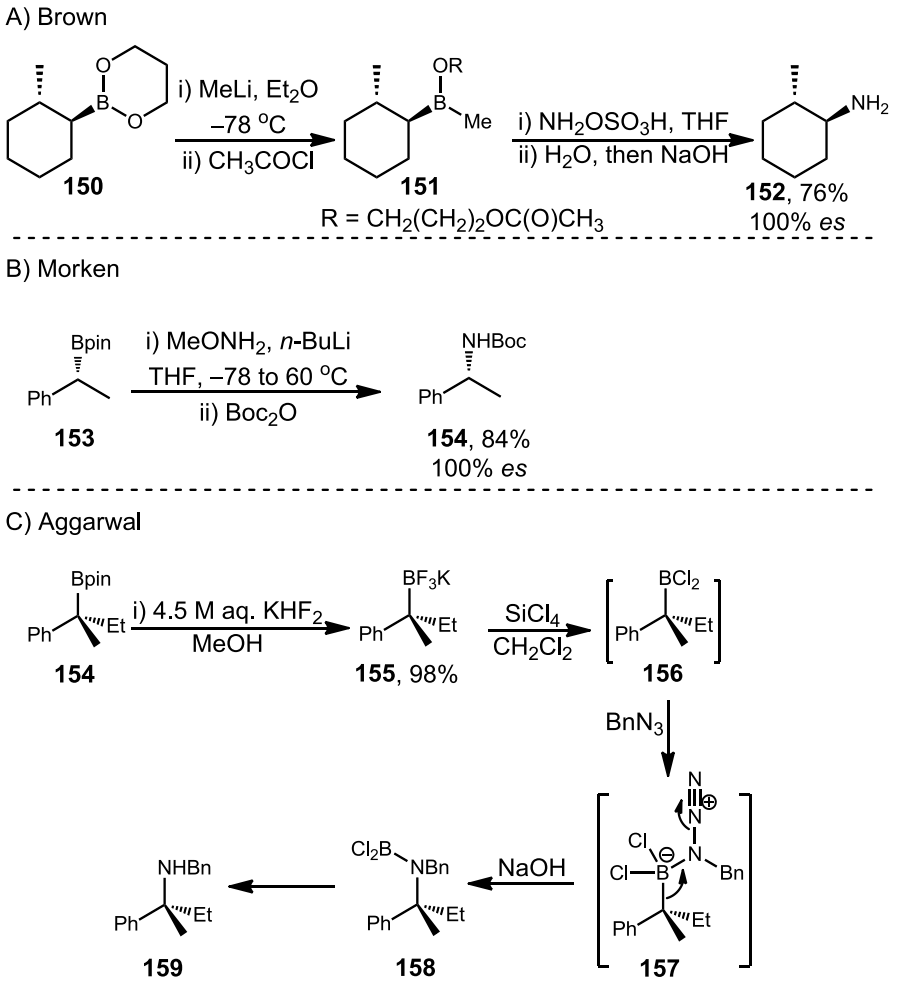
### 1.4.1. Carbon-heteroatom bond formation

The oxidation of enantioenriched boronic esters, affording the corresponding alcohols, is the most versatile and extensively applied transformation of the C-B bond. The oxidation is usually accomplished by employing basic hydrogen peroxide, firstly reported by Brown and coworkers in 1961.[73] The reaction consists of three steps, the first step is the attack of peroxide anion to the empty p-orbital on boron atom, leading to the formation of boronate complex **147**; sequently the 'ate' complex **147** undergo 1,2-metalate rearrangement, with the carbon substituent migrating to the adjacent oxygen atom and loss of hydroxide. Final hydrolysis of trialkyl boronate **148** delivers alcohol **149** with complete stereoretention (Scheme 1.23). Alternative oxidation methods utilising reagents such as sodium perborate,[74] oxone[75] and trimethylamine *N*-oxides[76] have also been developed.




**Scheme 1.23.** Mechanism of oxidation of boronic esters by basic hydrogen peroxide.

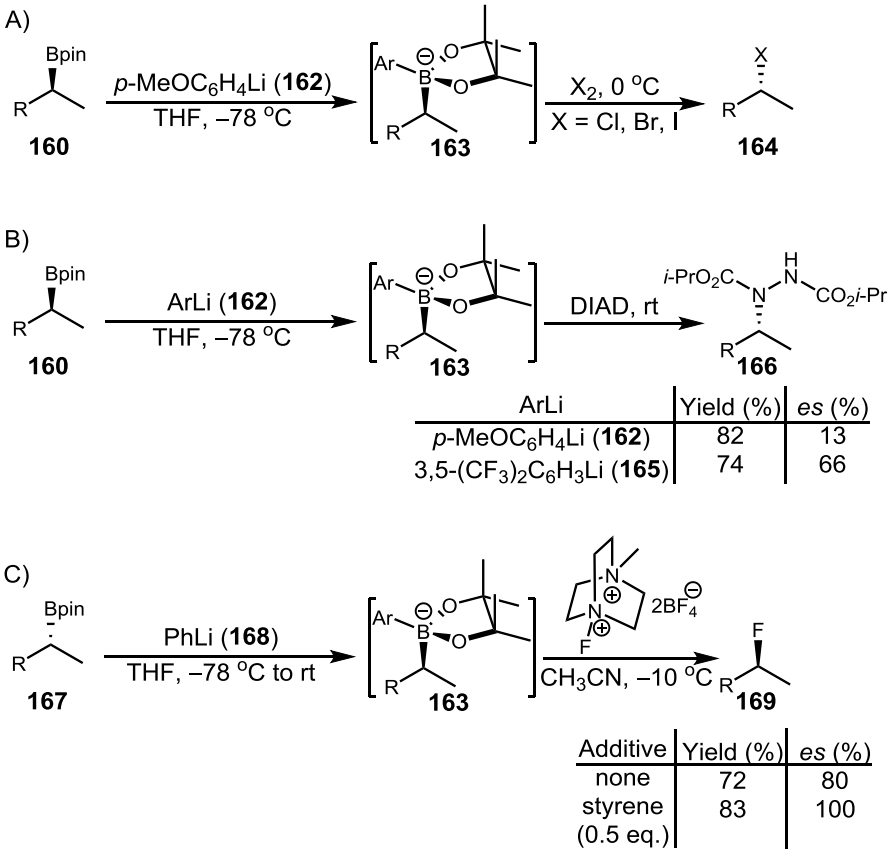
With respect to the amination of organoboron compounds, trialkylboranes can be readily transformed into the corresponding amines with various reagents such as chloramine[77] or alkyl azides.[78,79] Whereas the amination of boronic esters did not proceed well using these reagents owing to the ineffective association resulting from the reduced Lewis acidity. In 1986, Brown and coworkers successfully facilitated the stereospecific amination of boronic esters **154**, by converting compound **150** to the borinic ester **151**, which was followed by amination using $NH_2OSO_3H$ (Scheme 1.24A).[80]




**Scheme 1.24.** Amination of secondary and tertiary esters.

Morken and coworkers reported the direct amination of secondary boronic esters using methoxy amine and *n*-BuLi.[81] The desired *N*-Boc protected amine **154** was afforded in good yield and excellent stereospecificity (Scheme 1.24B). Nevertheless, the amination of tertiary boronic esters was not effective under these conditions. Aggarwal and coworkers successfully demonstrated the stereospecific amination of tertiary boronic esters. The reaction proceeded in two steps via an intermediate trifluoroborate salt **155**,[82] which was prepared by fluorination using $KHF_2$ in MeOH.[83] The subsequent reaction of compound **155** and $SiCl_4$ delivered alkyl dichloroborane **156**, which was further treated with alkylazide to form the corresponding amine **159** with full stereoretention (Scheme 1.24C). It is noteworthy that this reaction can occur intramolecularly and is applicable to non-benzylic boronic etsers.[68]

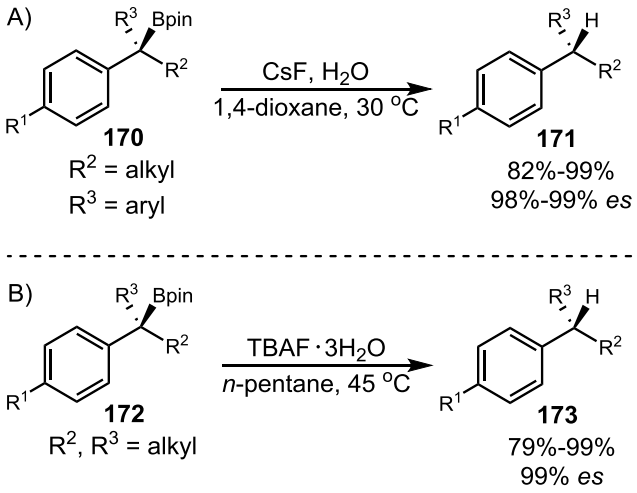
In addition, Aggarwal and coworkers discovered that chiral boronic esters can serve as precursors to chiral nucleophilic reagents, which can react with various electrophiles.[84-85] The reaction was accomplished by the formation of boronate complex **162**, and subsequent substitution of electrophiles (Scheme 1.25), which resulted in the formation of C-X (X = Cl, Br, I), C-N and C-O bonds.[84] Reactions with halogens could afford the desired product **164** with high enantiospecificity via a $S_E2inv$ pathway (Scheme 1.25A). However, in the case of DIAD, a competing single-electron transfer (SET) pathway was involved, leading to low stereospecificity. Adjusting the selection of aryllithium, the SET pathway can be reduced resulting in an increase in enantiospecificity (Scheme 1.25B). The range of halogen reagents can be expanded to include fluorine.[85] In this process, Selectfluor II was chosen as the electrophile, which reacted with the *in situ* generated boronate complex **162** to give alkylfluoride **169** in high yield and excellent stereospecificity. Notably, styrene was found to be enhance the enantiospecificity of the process (Scheme 1.25C).




**Scheme 1.25.** reactions of nucleophilic boronate complex with electrophiles.

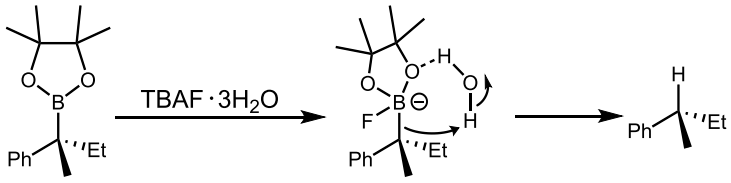
### 1.4.2. Carbon-hydrogen bond formation

Stereospecific protodeboronation of tertiary boronic esters can accomplish the efficient synthesis of tertiary alkyl stereogenic centres.[57] The use of CsF and $H_2O$ at 30 °C can successfully trigger the protodeboronation of diaryl alkyl boronic ester **170**, delivering the desired product **171** in excellent yield and *es* (Scheme 1.26A). On the contrary, the aryl dialkyl boronic ester **172** was found to be significantly difficult to undergo protodeboronation under these conditions. However, the use of more reactive TBAF·3$H_2O$ in place of CsF in *n*-pentane at 45 °C can effectively generate the protodeboronated product **173** in good yield and *es* (Scheme 1.26B). It is noteworthy that activated boronic esters, such as benzylic or allylic[39] boronic esters, are required under these conditions. Nevertheless, the protodeboronation of non-benzylic boronic esters can be achieved by adopting oxidative conditions, resulting in the cleavage of the C-B bond, with loss of stereospecificity due to the radical pathway.[86-88]




**Scheme 1.26.** Protodeboronation of tertiary boronic esters.

With respect to the mechanism of the TBAF·3$H_2O$ reaction, a $H_2O$ hydrogen-bonded boronate complex is believed to be the key intermediate, which places the proton on the same side of boron atom, thereby leading to high stereoretention (Scheme 1.27).

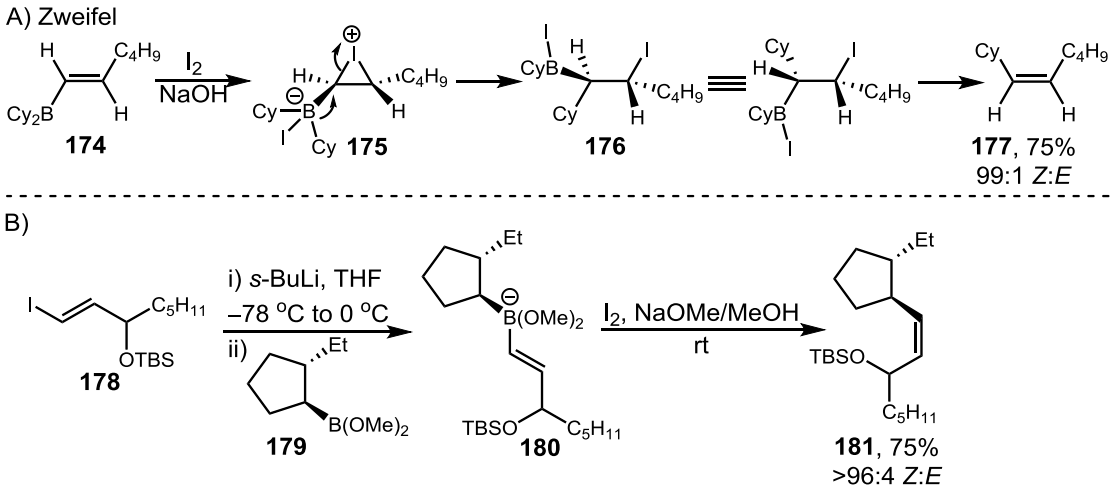



**Scheme 1.27.** Proposed mechanism for the TBAF mediated protodeboronation of tertiary boronic esters.

### 1.4.3. Carbon-carbon bond formation

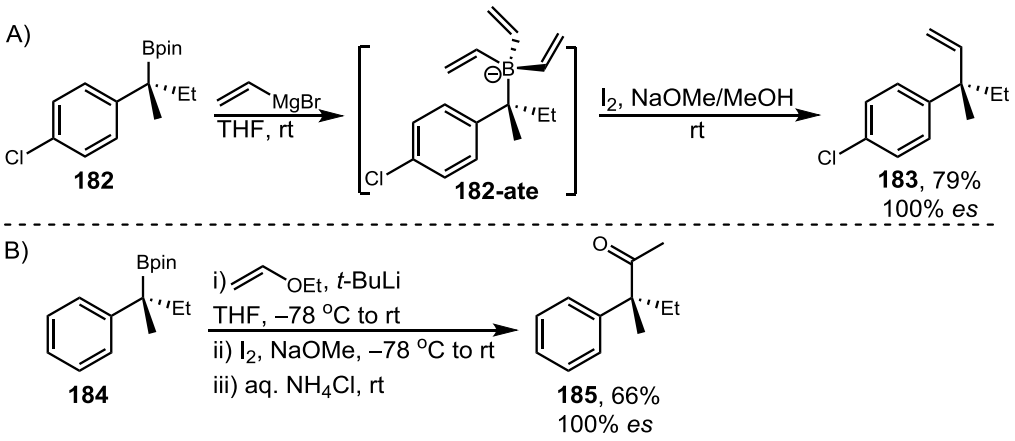
An interest in the possibility of generating new C-C bond is increasingly focused on the further homologations of boronic esters. Part of the research includes the Matteson homologation and the lithiation–borylation reactions with carbamates or TIB esters, which have already been described in chapter 1.1 and 1.3, respectively.

Chiral boronic esters can also undergo a stereospecific transformation to afford the corresponding alkenes. Zweifel and coworkers reported their seminal research on the selective formation of a single alkene isomer using boranes in 1967.[89] The authors found that vinyl borane **174** could be converted into alkene **177** in good yield as a *Z* isomer employing iodine under basic conditions. For the reaction mechanism, the reaction of iodine and vinyl borane **174** forms the iodonium ion **175**. Subsequently one alkyl substituent on boron atom undergoes stereospecific 1,2-migration and generates iodo-borane **176**. The attack of base to the boron atom leads to the deboronation of compound **176** and finally delivers the *Z*-alkene **177** (Scheme 1.28A). Evans and coworkers discovered that this reaction can be carried out with boronic ester **179** and *in situ* generated vinyllithium, affording *Z*-type alkene **181** exclusively (Scheme 1.28B).[90]




**Scheme 1.28.** Early examples of Zweifel olefination on boranes and boronic esters.

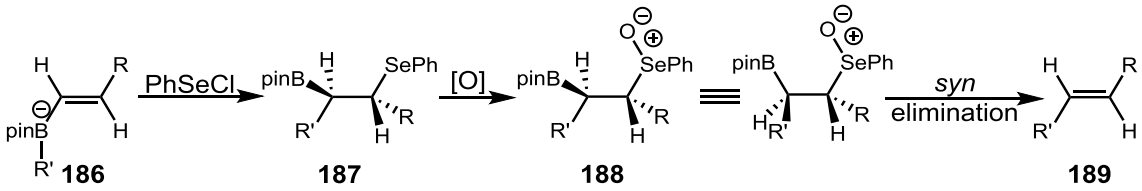
Aggarwal and coworkers broadened the application of this methodology, and successfully transformed enantioenriched tertiary boronic esters into terminal alkenes with excellent stereospecificity employing excess of Grignard reagent–vinylmagnesium bromide (Scheme 1.29A).[91] It was found that the reaction underwent formation of the boronate complex **182-ate** before giving the corresponding alkene **183**. Notably, employing ethoxy vinyllithium in the same course led to the formation of methyl alkyl ketone **185** (Scheme 1.29B).[68,91]




**Scheme 1.29.** Functionalisation of tertiary boronic esters using Zweifel olefination.

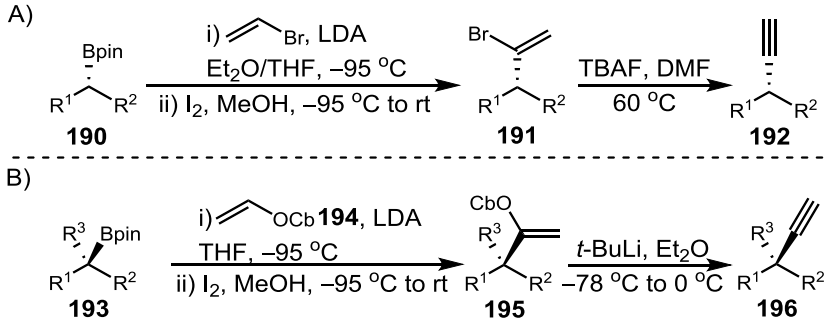
Recently, Aggarwal and coworkers developed the generation of *E*-type by use of PhSeCl instead of electrophile iodine.[92] Treatment of vinyl boronate complex **186** with

PhSeCl afforded β-selenoboronate **187**, which was selectively oxidised by *m*-CPBA to give selenoxide **188**. Subsequent *syn*-elimination of compound **188**, which is different from Zweifel *anti*-elimination (Scheme 1.28A), eventually delivered *E*-alkene **189** exclusively (Scheme 1.30).




**Scheme 1.30.** *E*-Selective Zweifel olefination.

In 2016, Aggarwal and coworkers reported the enantiospecific alkynylation of alkyl boronic esters affording chiral terminal alkynes.[93] Boronic ester **190** firstly undergoes a Zweifel olefination with lithiated vinylbromide (*in situ* generated in the presence of LDA at –95 °C) to afford bromo-alkene **191**. The following TBAF-mediated elimination further gives alkyne **192** in high yield and excellent *es* (Scheme 1.31A). Vinyl carbamate **194** was proved to be more effective with chiral tertiary boronic ester substrates. With the formation of intermediate **195** and subsequent elimination, alkyne **196** was isolated in excellent yield and enantiospecificity (Scheme 1.31B).

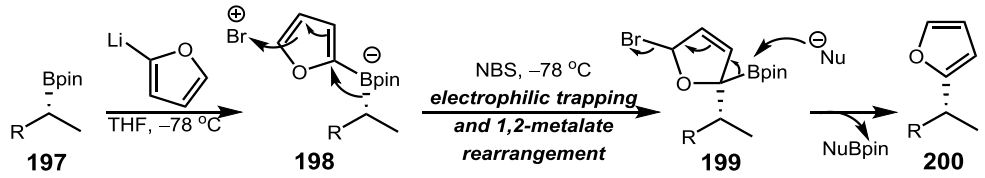



**Scheme 1.31.** *E*-Selective Zweifel olefination.

The enantioenriched secondary and tertiary boronic esters were also exploited in the extensively established Suzuki-Miyaura reactions. In 2009, Crudden and coworkers reported the first palladium-catalysed stereospecific cross coupling of secondary

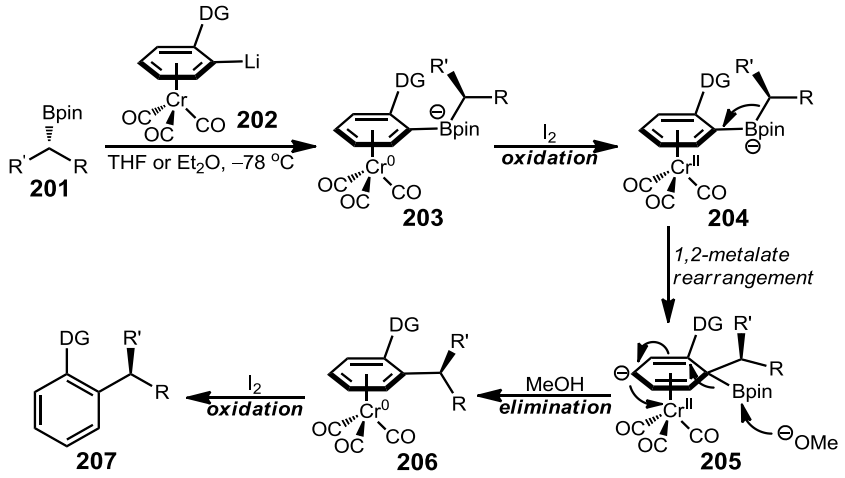
benzylic[94,95] and dibenzylic boronic esters.[96] The reaction was proved to be configurationally retentive. Recently, Liao and coworkers demonstrated that the cross coupling of trifluoroborate salts with aryl triflates proceeded with inversion of configuration.[97] In 2014, Biscoe and coworkers successfully developed the first enantiospecific Suzuki-Miyaura coupling of unactivated trifluoroborate salts, which furnished the corresponding product in excellent *es*.[98]

Aggarwal and coworkers reported the $sp^2$-$sp^3$ coupling of chiral boronic esters and aromatic compounds under transition-metal-free conditions (Scheme 1.32).[59,99] With this strategy, boronate complex **198** was formed by reaction of lithiated furan and boronic ester **197**, which, after activated by NBS, further underwent 1,2-metalate rearrangement to deliver intermediate **199**. Final deboronation with nucleophiles gave the desired product **200** with excellent enantiospecificity. It is noteworthy that the reaction scope can be extended to the challenging tertiary boronic esters, and the furan can also be substituted by a variety of electron-rich aromatics as well as *N*-heteroaromatic[100] and phenols.[101]




**Scheme 1.32.** Transition-metal-free $sp^2$-$sp^3$ coupling of chiral boronic esters with furan.

In 2018, the $sp^2$-$sp^3$ coupling of chiral boronic esters and aromatics without activating groups was developed by Aggarwal and coworkers.[102] In this process, boronic ester **201** was treated with lithiated chromium arene **202** to form boronate complex **203**. Subsequently, oxidation of the boronate complex **203** by iodine generated chromium (II) complex **204**, leading to the formation of sufficiently electron-deficient aryl ring, which made the following 1,2-metalate rearrangement proceed smoothly to afford anion **205**. The methanol-mediated elimination and oxidation with iodine finally delivered the desired product **207** with high yield and enantiospecificity. The methodology proved to be versatile and a broad range of various substituted arenes and secondary boronic esters were employed in the reactions.




**Scheme 1.33.** Enantiospecific $sp^2$-$sp^3$ coupling of boronic esters with furan with chromium arene complex.

## *1.5. Conclusions*

The lithiation–borylation reaction has proved to be a versatile and powerful methodology for the homologation enantioenriched boronic esters. The methodology has already been applied into the synthesis of complex natural products, which bear several successive tertiary or quaternary stereogenic centres. Numerous developments have been achieved to improve the reaction and to broaden its application scope.

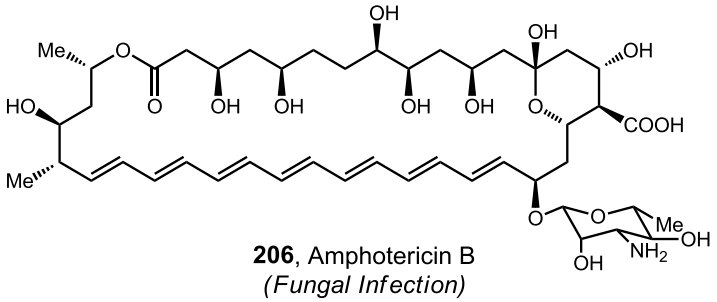
The work presented in this thesis aims at further broadening the applications of the lithiation-borylation methodology, mainly focusing on two aspects: the coupling of readily prepared building blocks (acceptor: benzoate ester and donor: organoboronic ester) to synthesise a polypropionate fragment using lithiation-borylation, and explorations into the introduction of difluoromethyl group and monofluoromethyl group by lithiation-borylation reactions of organoboronic esters.

# 2. Stereocontrolled Synthesis of Polypropionate Fragment Based on Building Block Assembly Strategies by Lithiation–Borylation Methodologies

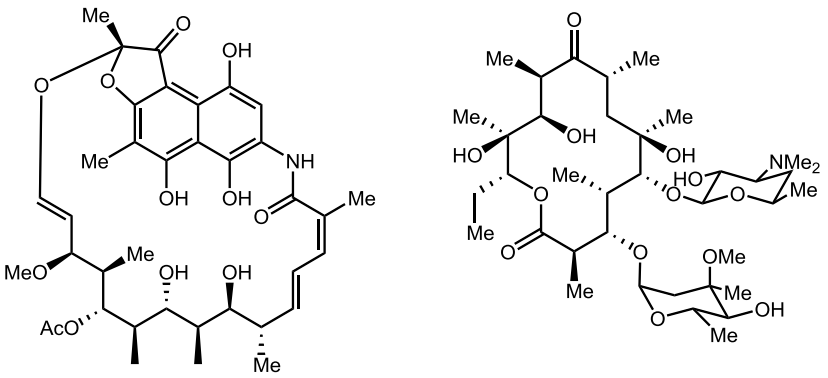
## *2.1. Introduction and Project Aims*

The term *polyketide* was introduced into the chemical literature in 1907 by John Norman Collie. Collie proposed that ketene ($CH_2$=C=O) or its hydrolysis product, acetic acid, was the basic building block for a great number of aromatic plant metabolites, hence the designation, *polyketide*.[103]

Polyketides are a very important class of secondary metabolites in nature that display a broad spectrum of biological activity, such as antibiotics, antitumoral, antifungal, antiparasitic and immunomodulatory.[104] Due to their diverse bioactivity and pharmaceutical properties, polyketides have been used extensively in human medicine.[104-107] Approximately 20% of the top-selling small molecule drugs are polyketides,[106-108] and it is estimated that polyketides are five times more likely to possess drug activity compared to other natural product families.[108] The first commercial polyketide drug, erythromycin A, a macrolide antibiotic isolated from soil bacteria from the Philippines, was marketed by Eli Lilly in 1952.[109] In 1955, amphotericin B, an important anti-fungal drug, was discovered in soil samples taken from Venezuela,[110-112] and shortly thereafter, rifamycin B, which inhibited drug-resistant tuberculosis in the 1960s,[113-116] was isolated from soil samples taken from the south of France (Figure 2.1).




**206**, Amphotericin B
*(Fungal Infection)*

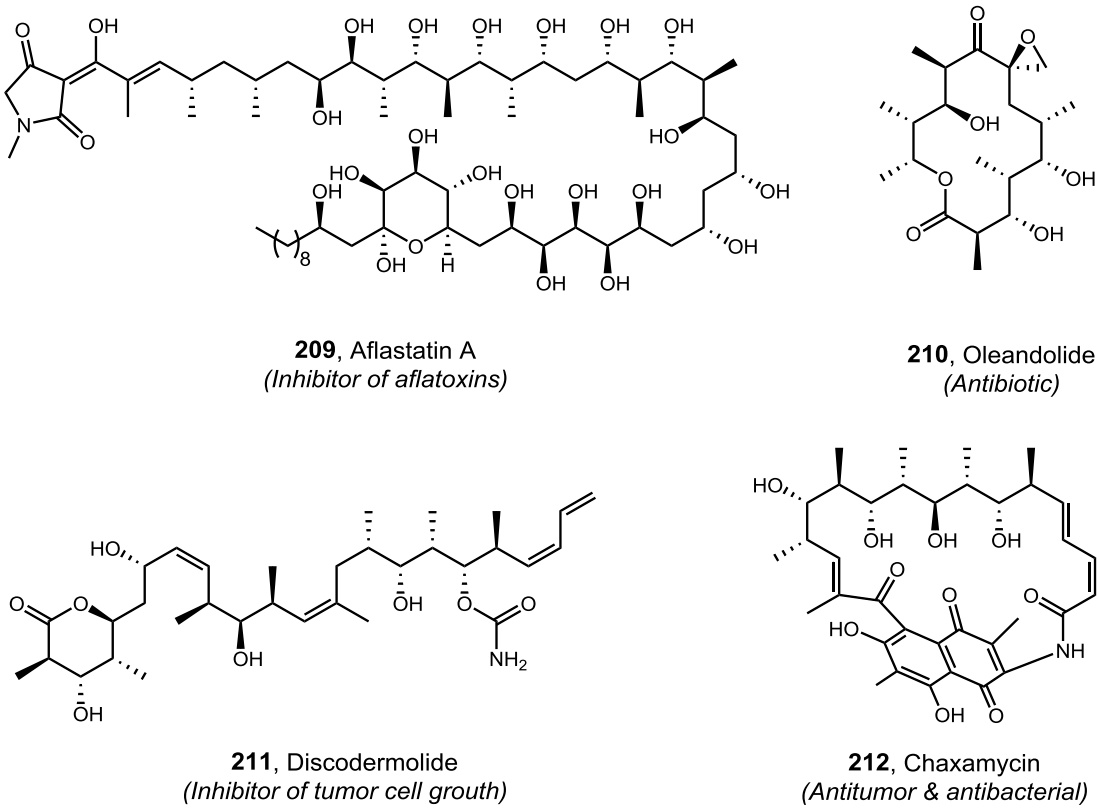


**207**, Rifamycin B
*(Mycobacterial Infection)*

**208**, Erthromycin A
*(Bacterial Infection)*

**Figure 2.1.** Representative polypropionate natural products

Polyketides are classified according to their structures and biochemical origins into three major classes, which are fatty acids, polypropionates, and aromatics polyketides. Polypropionates constitute the structurally widest subclass of polyketides. They are characterised by sequences of methyl- and hydroxyl-bearing stereogenic centres, enabling large numbers of possible stereochemical permutations (Figure 1.2**)**.



**209**, Aflastatin A
*(Inhibitor of aflatoxins)*

**210**, Oleandolide
*(Antibiotic)*

**211**, Discodermolide
*(Inhibitor of tumor cell grouth)*

**212**, Chaxamycin
*(Antitumor & antibacterial)*

**Figure 2.2.** Representative polypropionate natural products

The importance of these natural products as therapeutic agents and as biomedical tools together with their structural complexity has made these molecules attractive targets for synthetic organic chemists. The key to constructing these systems, which possess a high level of stereochemical information, is the control of the absolute and relative stereochemistry of each centre.

### 2.1.1 The Preparation of Polypropionates

In Nature, polypropionates are biosynthetically assembled by polyketide synthase via iterative condensation of propionyl subunits and subsequent reduction of the derived β–keto esters (Figure 2.3).

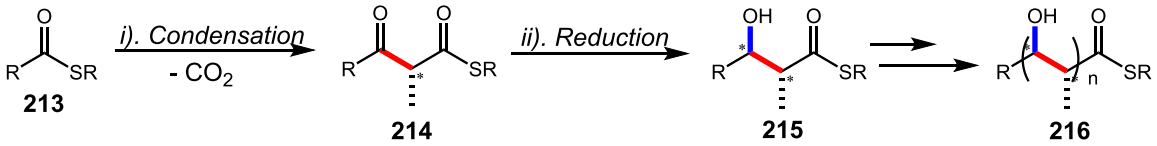



**Figure 2.3.** Elementary steps in polypropionate biosynthesis

Mimicking this biosynthetic pathway, the aldol reaction presents the most important method available for the stereocontrolled formation of propionates and many variants for regio-, stereo-, and enantioselective carbon-carbon bond formation have been reported.

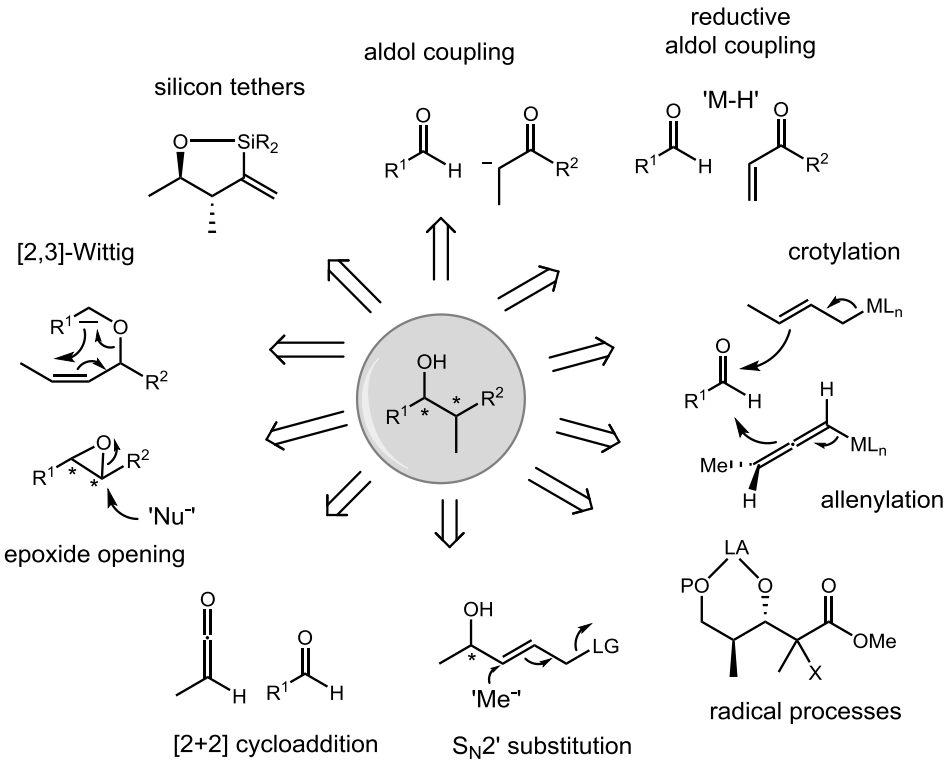
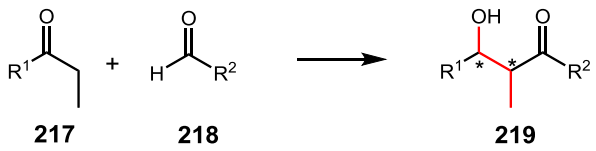



**Figure 2.4.** Methods for polypropionate synthesis

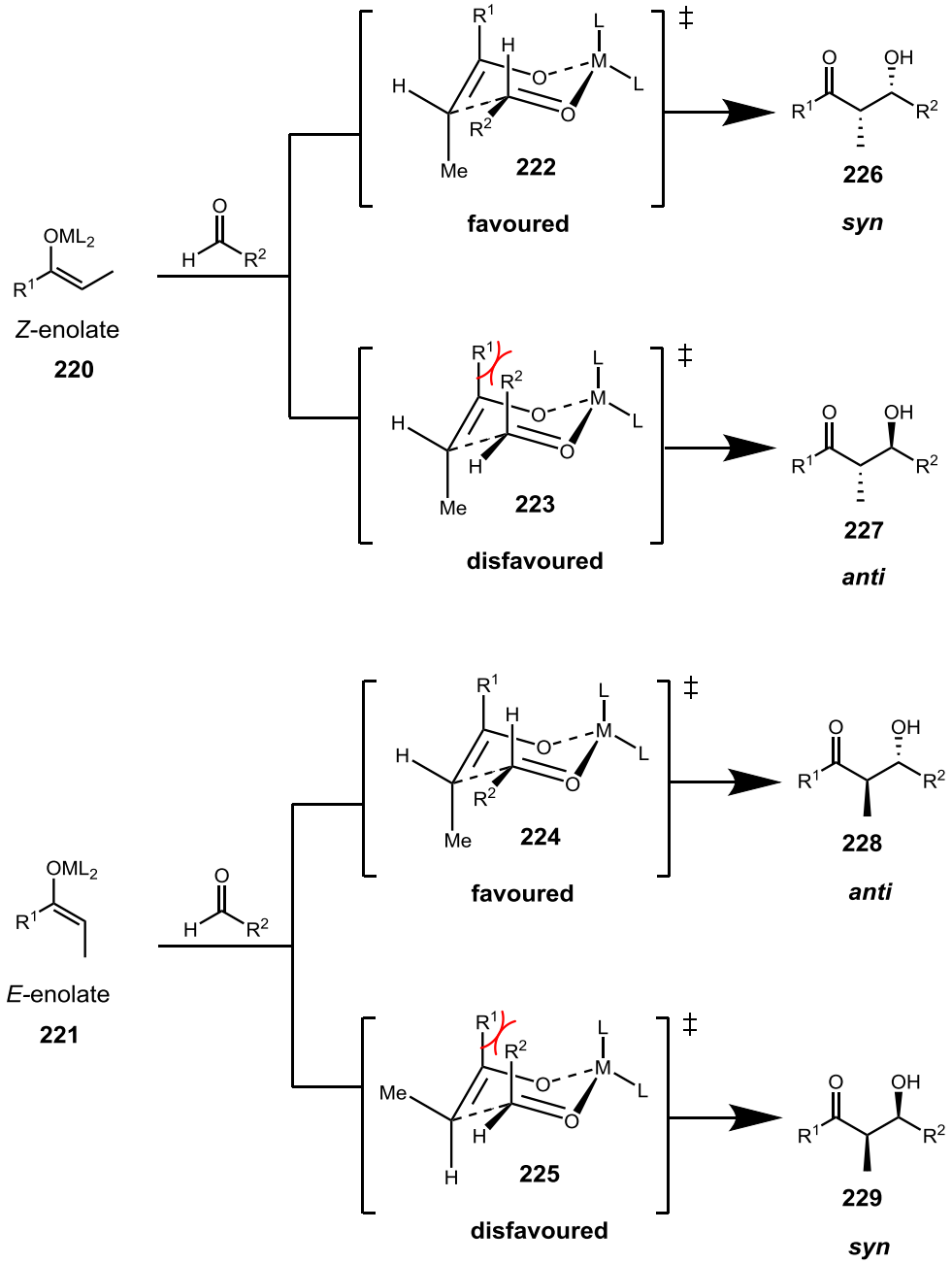
Furthermore, alternative strategies of increasingly high importance have been reported,[117] such as crotylation reactions (Figure 2.4). In the following section, a general introduction to the aldol reaction, and some variants of the crotylation reaction will be presented.

*Aldol Reaction*

The aldol addition reaction continues to be a highly versatile and widely used method for the selective synthesis of polypropionates.[118-125] The addition reaction involves the condensation of ethyl ketones **217**, including esters or amides, with aldehydes **218** to generate the required chiral β-hydroxy carbonyl adducts **219** in a direct fashion (Scheme 2.1).




**Scheme 2.1.** Aldol reaction in polypropionate synthesis.




**Scheme 2.2.** Transition states analysis of aldol reactions.

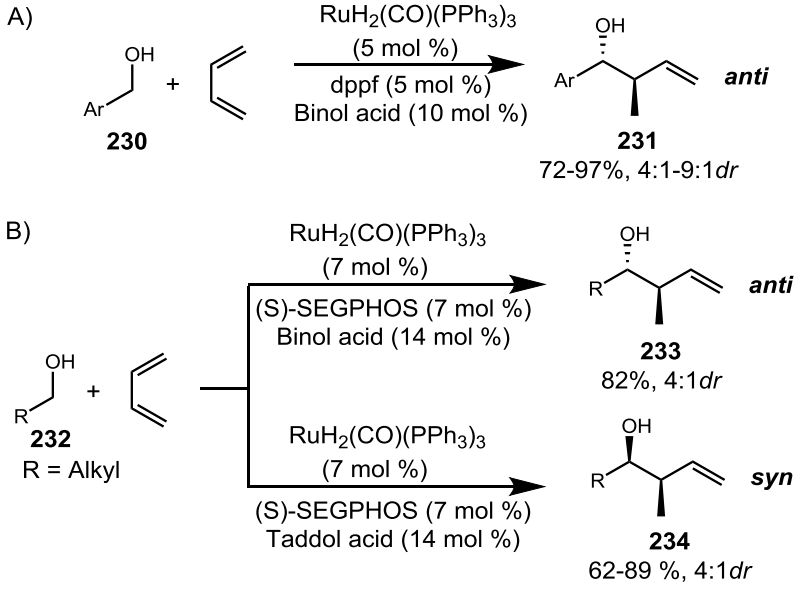
The relative configuration of the aldol adduct is usually determined by the geometry of the enolate intermediate, with *Z*-enolates **220** giving *syn* products **226** and *E*-enolates **221** *anti* products **228**. As shown in Scheme 2.2, this result has been rationalised by closed transition state models as reported by Zimmerman and Traxler. Minimisation of 1,3-diaxial interactions between $R^1$ and $R^2$ in the chair-like transition states **222** versus **223** and **224** versus **225** leads to the observed stereochemical outcome (Scheme 2.2).[126]

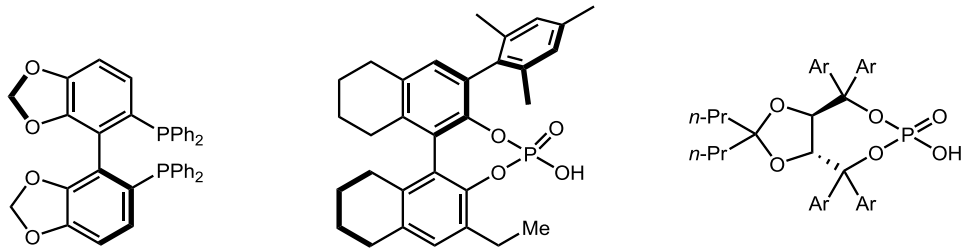
Although aldol type reactions are widely applied in the synthesis of polypropionates, there may be some difficulities in synthesising specific diastereoisomers due to the mismatched effects caused by substrate bias.

*Crotylation Reactions*

*Krische's metal catalysed C-H crotylation*

Metal catalysed carbonyl crotylation reactions can also be applied in the synthesis of polypropionates. Krische and co-workers have performed extensive studies in this area. In 2012, Krische and co-workers reported the ruthenium-catalysed enantioselective C-H crotylation of primary benzylic alcohols,[127] which afforded the product in good yield and moderate diastereoselectivity via hydrohydroxyalkylation of butadiene (Scheme 2.3A). Later in the same year, they reported studies which developed the enantioselective crotylation to primary aliphatic alcohols (Scheme 2.3B).[128] In this work, the stereoselectivity could be tuned by changing the chiral counterion. Furthermore, iridium could also be used to catalyse the crotylation of alcohols.

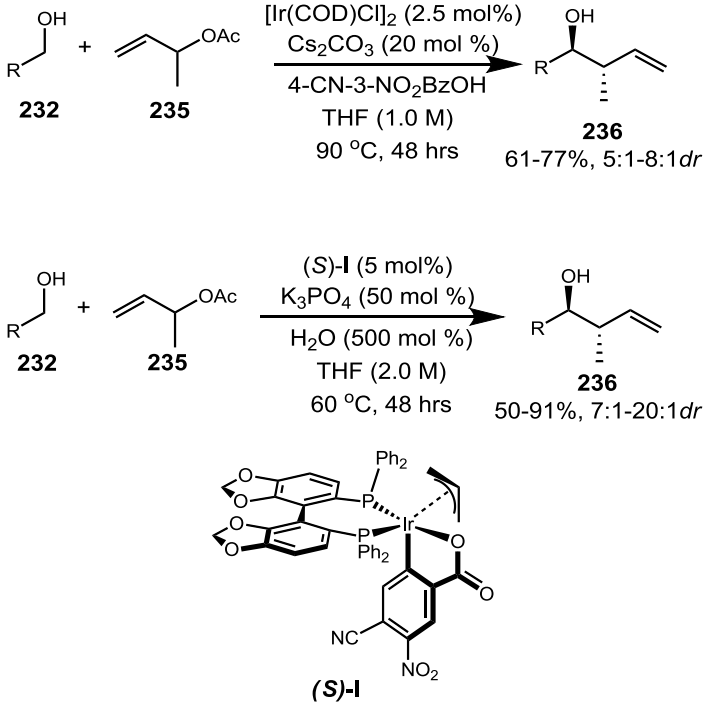




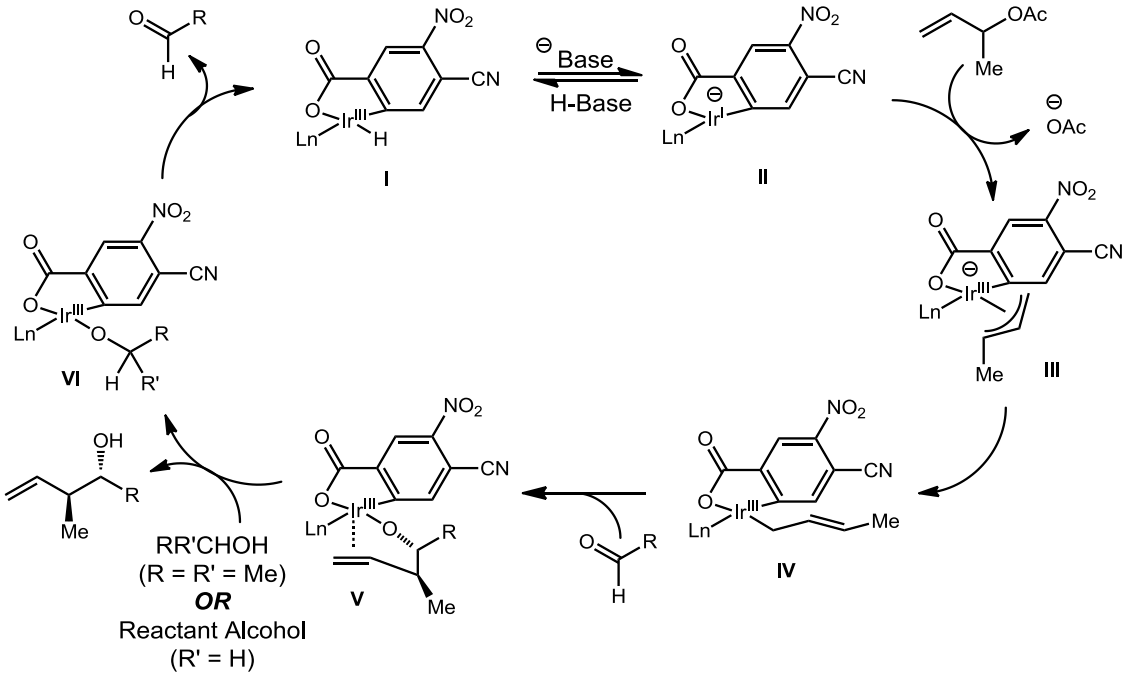

**235**, (*S*)-Segphos **236**, Binol acid **237**, Taddol acid

**Scheme 2.3.** Ruthenium-catalysed crotylation reaction.

In 2009 and 2011, the Krische group realised the enantioselective crotylation of alcohols with in-situ generated or isolated iridium catalysts (Scheme 2.4).[129,130] Both benzylic and aliphatic alcohols could be employed as substrates. Although *in situ* generation of the catalyst is convenient and exceptional enantioselectivities were observed, moderate levels of anti-diastereoselectivity were observed (Scheme 2.4). It was found that the chromatographically purified catalyst functions at lower temperature, resulting in enhanced levels of anti-diastereoselectivity (Scheme 2.4). Compared with ruthenium, iridium catalysed crotylation reactions could afford better diastereoselectivity.




**Scheme 2.4.** Iridium catalysed crotylation reaction.

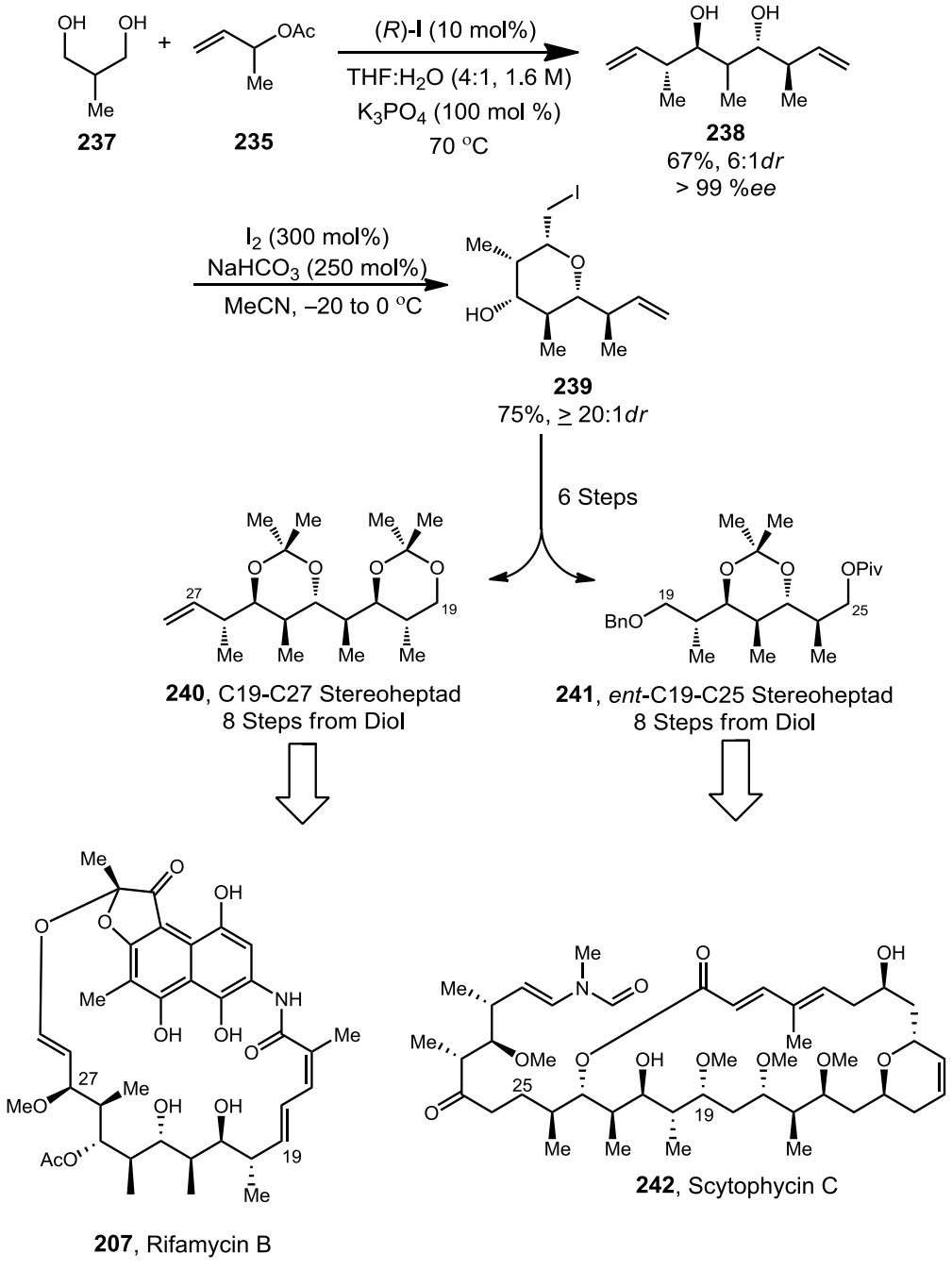


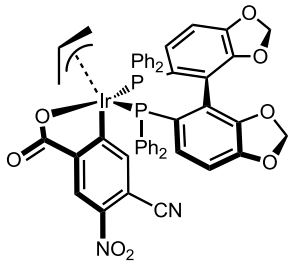

**Scheme 2.5.** The mechanism of iridium catalysed crotylation reaction.

The mechanism for the iridium-catalysed crotylation is depicted in scheme 2.5.[129] The *ortho*-cyclometallated iridium hydride **I** undergoes deprotonation in the presence of base to furnish the anionic iridium (I) *C,O*-benzoate **II**. Oxidative addition to α-methyl allyl acetate delivers the iridium *π*-crotyl complex **III**. Aldehyde addition by way of the (*E*)-*σ*-crotyl-iridium complex **IV** through a closed chair-like transition structure delivers the *anti*-homoallyl iridium alkoxide **V**. This intermediate is stable with respect to β–hydride elimination of the carbinol C-H due to occupation of the remaining coordination site at iridium (III) by the olefin moiety of the homoallylic alcohol. Exchange of the homoallyl alcohol for a reactant alcohol provides **VI**, which has an open coordination site and, consequently, β-hydride eliminates to regenerate the *ortho*-cyclometallated complex **I**.

The iridium catalysed crotylation reactions were then successfully applied in the synthesis of polypropionates. The rapid generation of polyacetate substructures via iterative double allylation of 1,3-propanediol prompted an investigation into related double crotylations of 2-methyl-1,3-propanediol.[131] In the event, the chromatographically purified iridium precatalyst modified by (*R*)-SEGPHOS delivers

the product of double crotylation as predominantly 1 of 16 possible stereoisomers due to the amplification effect.[132,133] The resulting pseudo-C2-symmetric polypropionate stereoquintet possesses a chirotopic non-stereogenic centre at the central carbon atom. Iodoetherification defines this stereocentre and differentiates the two terminal olefin and two secondary alcohol moieties. With the iodoether in hand, the C19–C27 stereoheptad of rifamycin B was rapidly assembled (Scheme 2.6).[134] In a similar fashion, the indicated iodoether was converted to a scytophycin C substructure in nearly half the number of steps previously required (Scheme 2.6**)**.



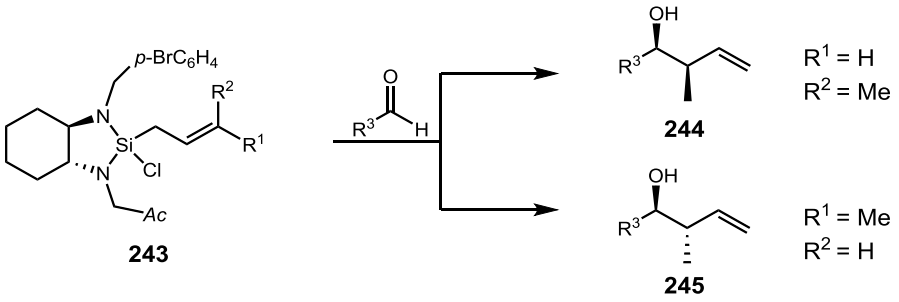



***(R)*-I**

**Scheme 2.6.** The synthetic application of iridium catalysed crotylation reaction

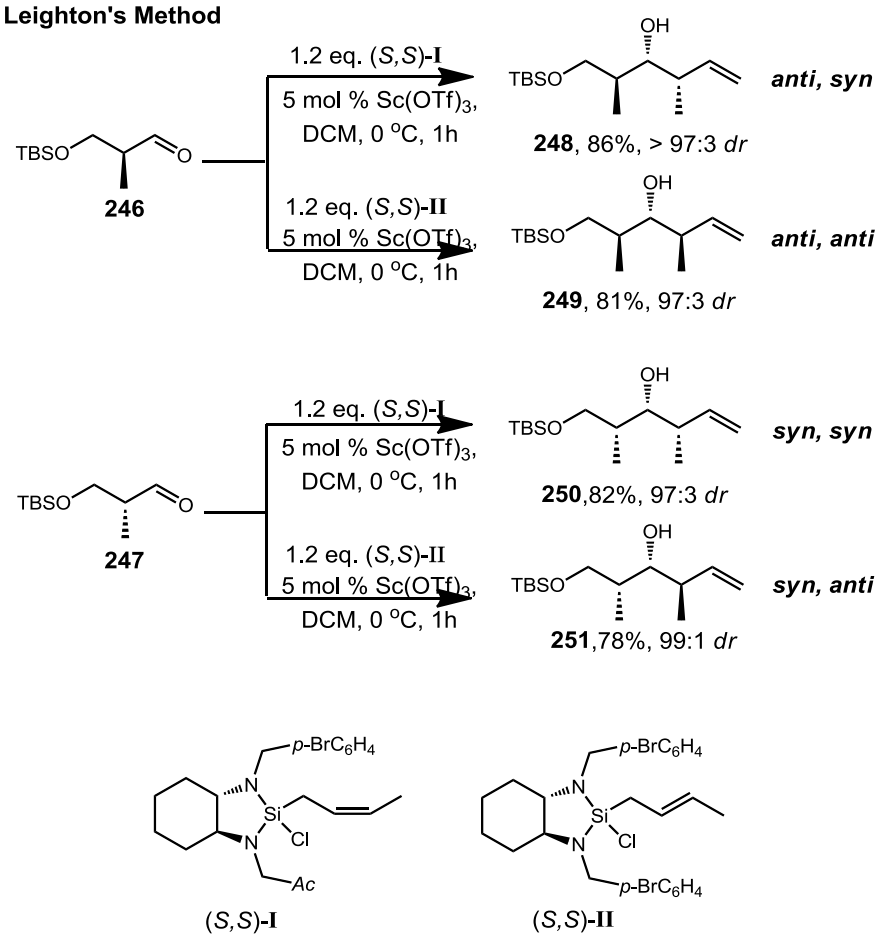
*Leighton's Si-Crotylation Reaction*

Chiral *cis*- and *trans*-crotylsilane reagents **243** (Scheme 2.7) have been developed by Leighton.[135] They are storable crystalline solids and can be prepared in bulk amounts, though their synthesis requires four steps. A survey of the performance of crotylsilane reagents was carried out with a variety of aliphatic, aromatic, and α,β-unsaturated aldehydes. In every case, the *cis*- and *trans*-crotylsilane reagents demonstrated their use in highly enantioselective *syn*- and *anti*-selective aldehyde crotylation reactions, respectively (Scheme 2.7). The crotylation reactions are experimentally trivial and the chiral diamine may be recovered.[136,137]




**Scheme 2.7.** Leighton's Si-Crotylation Reaction.

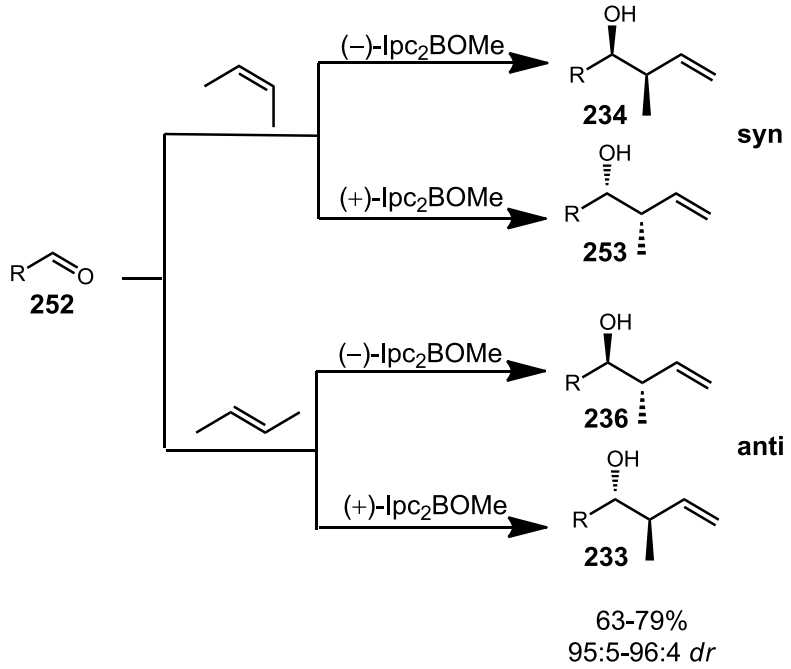
Scheme 2.8 highlights the excellence of Leighton's method. With this method, all four stereoisomers could be synthesised in excellent yield and diastereoselectivity.[138] The reactions were complete within only one hour at 0 $^{o}$C. However, issues remain with Leighton's method: the silyl reagents (*S, S*)-**I** and (*S, S*)-**II** used in reactions are not commercially available, and a small excess (1.2 equivalents) of the reagents are required in the reaction.




**Scheme 2.8.** Application of Leighton's crotylation reaction.

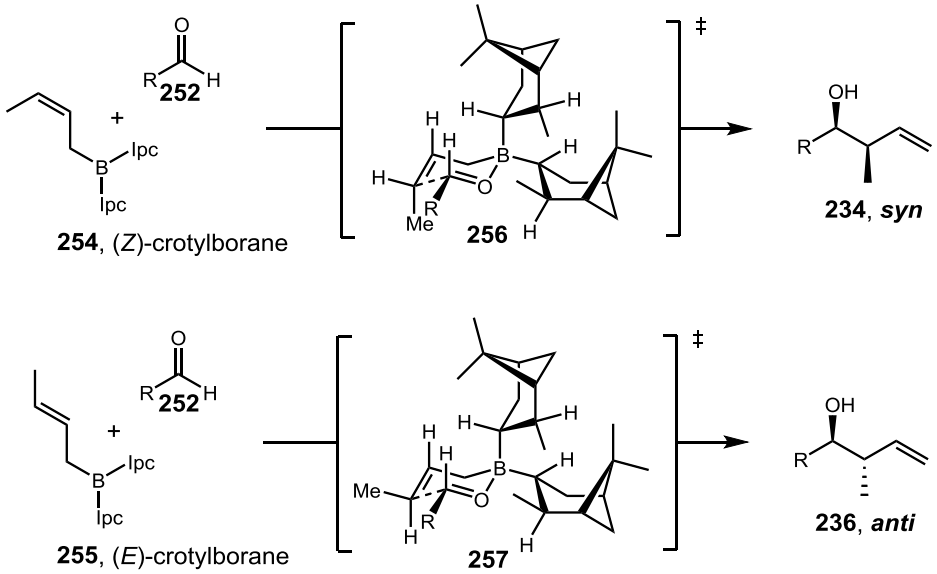
*B-Crotylation Reaction*

In 1986, Brown and co-workers developed the stereoselective crotylation of aldehydes utilising chiral borane reagents.[139,140] This reaction, making use of readily available chemicals, provided access to all four possible stereoisomers of the crotylation adducts by simply selecting either *(E)*- or (*Z*)-2-butene and the proper antipode of methoxydiisopinocampheylborane ($Ipc_2BOMe$). All stereoisomers could be afforded in excellent diastereoselectivity (Scheme 2.9).




**Scheme 2.9.** Brown's crotylation reactions

The reaction controls the diastereoselectivity via a chair-like transition state, where the boron atom is coordinated to the carbonyl oxygen. The aldehyde is oriented in such a manner that the R group is placed in an equatorial position of the chair to minimise the steric interactions between the isopinocampheol (Ipc) group on the boron atom and the allyl unit. The *syn*-alcohol could be obtained when using (*Z*)-crotylborate, while the *anti*-alcohol could be afforded when employing (*E*)-crotylborate (Scheme 2.10).[117]



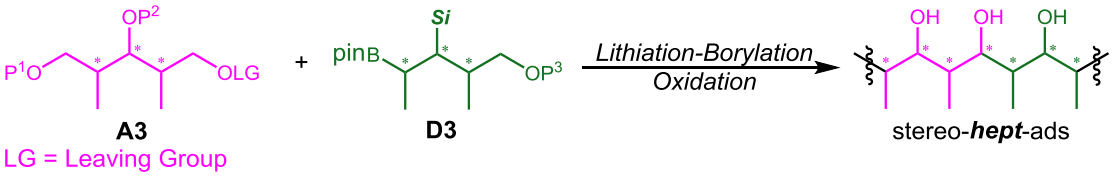

**Scheme 2.10.** Diastereoselectivity control of Brown's crotylation reaction.

In addition to Brown's carbonyl crotylation, Roush, Hoffmann and others have performed extensive studies on stereoselective boron-mediated crotylation reactions.[141-158]

### 2.1.2. Project Aims

The importance of polypropionates has made these compounds attractive targets for synthetic chemists for over four decades. The key to construct these polypropionate systems, which possess a high level of stereochemical information, is the control of the absolute and relative stereochemistry of each centre. However, whilst Nature's polyketide synthase assembles them by iterative condensations and reduction of propionyl subunits (see Figure 2.3), current methods mainly rely on aldol-type reactions.[15] Furthermore the synthesis of specific diastereoisomers can cause difficulties due to matched/mis-matched effects resulting from the substrate bias.

The lithiation–borylation methodology is ideally suited for the synthesis of polypropionates because full control of both relative and absolute stereochemistry can be achieved; moreover, with reagent–controlled stereoselectivity, the mis-matched effect can be avoided. We proposed acceptors **A3** (primary carbamates or benzoate esters), and the Donors **D3** (chiral boronic esters) which can produce polypropionate stereo-***n***-ads (Scheme 2.11); longer stereo-***n***-ads can also be prepared through further lithiation–borylation reactions. In this chapter, we intensively explored the lithiation–borylation reaction in polypropionate fragment synthesis, establishing suitable building blocks and reaction conditions.

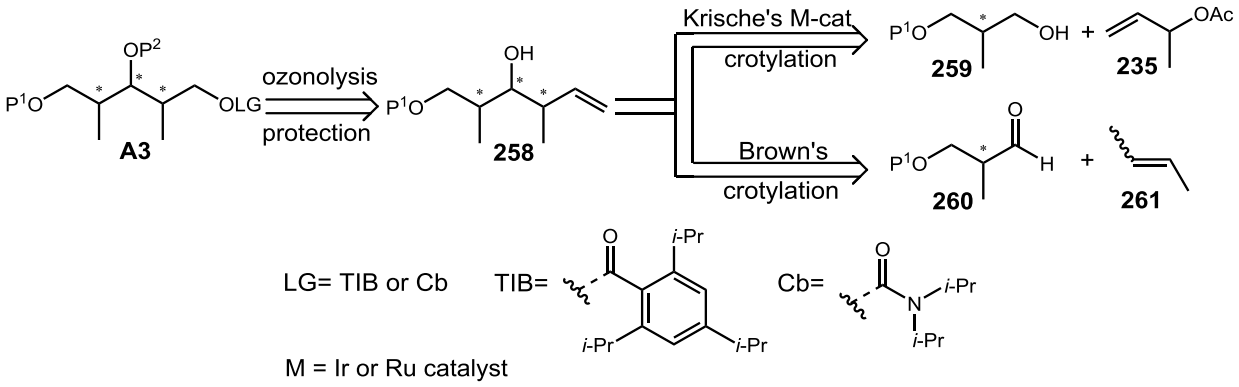



**Scheme 2.11.** Proposed Building Blocks.

## *2.2. Results and Discussion*

### 2.2.1. Preparation and Lithiation–Deuteration Studies of Alkyl *N*, *N*-Diisopropyl Carbamates.

As discussed in §.2.1.2 we decided to prepare stereotriads **A3** as building block for the synthesis of polypropionates using lithiation–borylation strategies. These types of compounds can be synthesised from the corresponding alkenes **258** (Scheme 2.12) by ozonolysis, installation of a leaving group and protection of the secondary alcohol. Olefin **258** can be prepared by several diastereoselective methodologies such as Krische iridium or ruthenium catalysed crotylation or Brown's boron-mediated crotylation reactions (See §.2.1.1 for further details) from the corresponding alcohol or aldehyde.



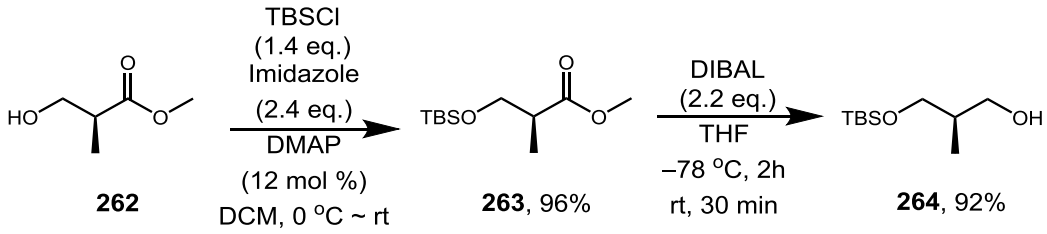

**Scheme 2.12.** Strategy for the synthesis of building blocks A3.

#### *2.2.1.1. Krische's Crotylation Reactions*

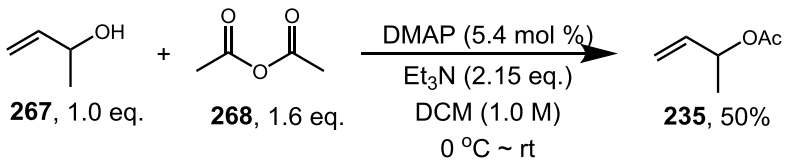
Initially, we focused on the iridium-catalysed crotylation reaction developed by Krische and co-workers for the synthesis of our set of alkenes. This methodology presents several advantages, including that the reactions employ crotyl acetate instead of the gas butadiene as the crotyl source, which is more convenient. These reactions also normally give better diastereoselectivity than the Ru-catalysed crotylation reactions developed by Krische and co-workers.

Alcohol **264** was synthesised as described in Scheme 2.13. From the commercially available (*S*)-Roche ester **262** we carried out the TBS protection of the primary hydroxyl group followed by reduction of ester **263** with DIBAL in excellent yield (Scheme 2.13A). Crotyl acetate **235** was prepared by acetylation of 3-buten-2-ol **267** in moderate yield (Scheme 2.13B).

A)

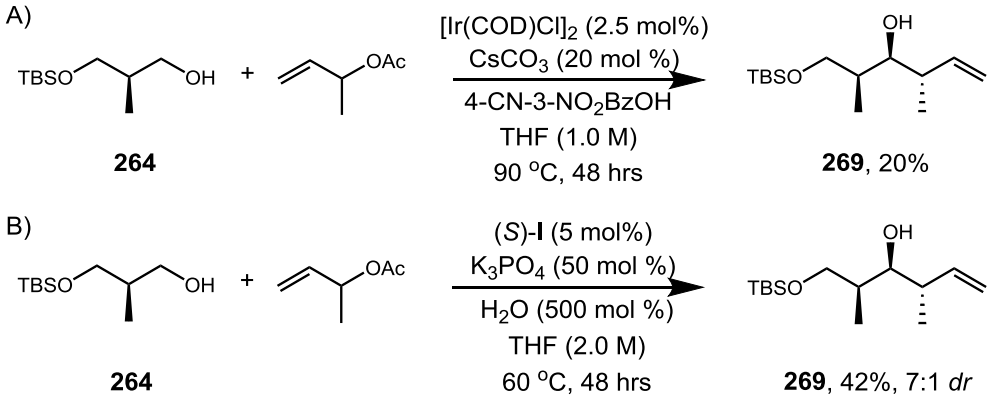



B)




**Scheme 2.13.** Synthesis of alcohol **264** and crotyl acetate **235.**

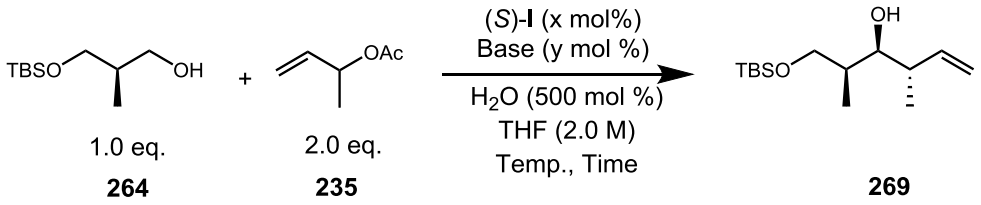
With both compounds in hand we tested the crotylation reaction under conditions reported by Krische and coworkers.[129,130] When the iridium-catalyst was generated *in situ*, a low yield was observed, but this result was improved when pre-synthesised iridium catalyst (*S*)-**I** (for structure see Scheme 2.4) was employed (Scheme 2.14).[130]




**Scheme 2.14.** Iridium-catalyzed crotylation reaction with alcohol **264**.

As starting material **264** was isolated in both experiments (~40%), we decided to screen different parameters such as reaction time, temperature, catalyst loading and the choice of base to increase the conversion and find the optimal conditions. Longer reaction times or slight increases in the temperature did not improve the yield substantially (Entry 1-3, Table 2.1). In contrast, when the reaction was carried out at 90 $^{o}$C the yield dropped (Entry 4, Table 2.1). The same effect was observed when catalyst loading was increased, which may result from the formation of a viscous reaction mixture. Finally, when increasing the amount of base (Entry 6-7, Table 2.1) or using $Na_2CO_3$ (Entry 7, Table 2.1) instead of $K_3PO_4$ lower yields were obtained.

**Table 2.1.** Optimization of Krische's crotylation reaction on alcohol **264** [a].

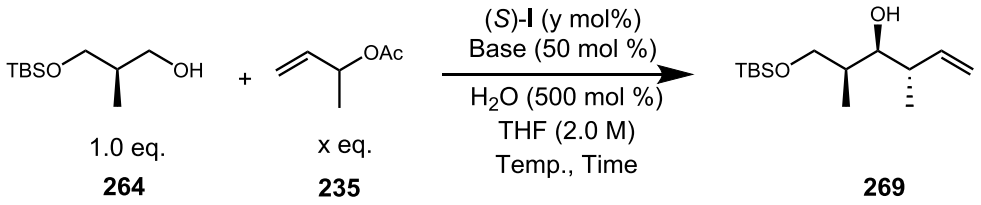



| Entry | Base | Catalyst (mol %) | Base (mol %) | Time (h) | Temp. ($^{o}$C) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $K_3PO_4$ | 5 | 50 | 48 | 60 | 42 |
| 2 | $K_3PO_4$ | 5 | 50 | 144 | 60 | 46 |
| 3 | $K_3PO_4$ | 5 | 50 | 48 | 70 | 48 |
| 4 | $K_3PO_4$ | 5 | 50 | 48 | 90 | 15 |
| 5 | $K_3PO_4$ | 10 | 50 | 48 | 60 | 28 |
| 6 | $K_3PO_4$ | 5 | 100 | 48 | 60 | 34 |
| 7 | $Na_2CO_3$ | 5 | 200 | 48 | 60 | 23[b] |

[a.] Reaction was performed on a 0.2 mmol scale; [b.] concentration is 1.0 M.

We also attempted to increase the equivalents of crotyl acetate (Table 2.2) with the hope that higher concentrations would accelerate the reaction and give a better yield, but this did not affect the yield substantially.

**Table 2.2.** Screening the effect of crotyl acetate equivalents on crotylation reaction [a].

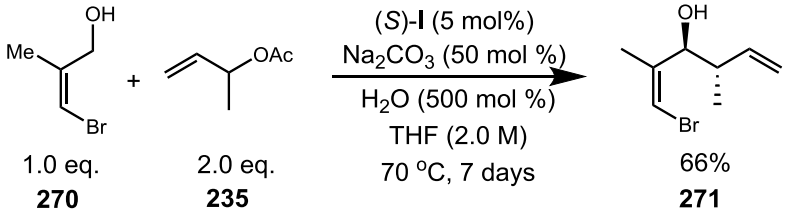



| Entry | Base | Catalyst (mol %) | Crotyl acetate (eq.) | Time (h) | Temp. (◦C) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $K_3PO_4$ | 5 | 2.0 | 48 | 60 | 42 |
| 2 | $K_3PO_4$ | 5 | 5.0 | 48 | 60 | 52 [b] |
| 3 | $K_3PO_4$ | 5 | 10.0 | 48 | 60 | 47 |

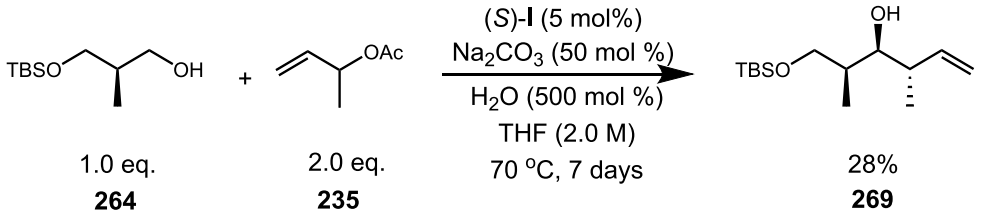
[a.] Reaction was performed on a 0.2 mmol scale; [b.] the yield was determined by $^1$H NMR.

It is noteworthy that linear alcohols are employed in most instances of iridium-catalysed crotylation reactions.[129,130] However, there is one example in the literature where Krische and co-workers carried out the crotylation reaction using a branched alcohol **270**, affording the corresponding product **271** in good yield (Scheme 2.15A).[159] We therefore applied their reported conditions to our case but unfortunately the reaction did not work well (Scheme 2.15B).

A)



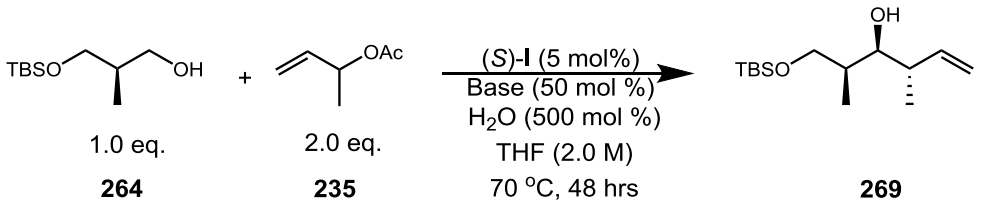

B)




**Scheme 2.15.** Iridium-catalysed crotylation reactions employing branched alcohols**.**

Although the reactions were set up in sealed tubes, we observed a decrease in the volume of the solvent that led to viscous reaction mixtures. Then we decided to compare different sealed tubes (see picture A-C, Table 2.3) to prevent the evaporation of the solvent and probe the influence on the final yields. As shown in Table 2.3, when longer tubes were used a slightly higher yield was obtained, but we can conclude that the effect is minimal.

**Table 2.3.** Effect of reaction tube size on crotylation reaction.




A: 8 cm B: 12 cm C: 18 cm

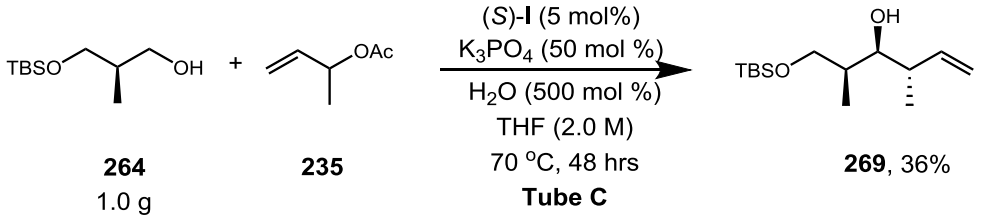
| Entry | Reaction tube | Time (h) | Temp. (°C) | Yield (%) [a] |
|---|---|---|---|---|
| 1 | A | 48 | 70 | 50 |
| 2 | B | 48 | 70 | 51 |
| 3 | C | 48 | 70 | 55 (49[b]) |

[a.] Yield was determined by 1H NMR with 1,4-dinitrobenzene as internal standard.;

[b.] Isolated yield.

After deep exploration, the optimal conditions were those in entry 3 of table 2.3, conducting the reaction in an 18-cm sealed tube at 70 °C employing 1.0 equivalent of alcohol **264** and 2.0 equivalents of crotyl acetate **235** in the presence of (*S*)-**I** catalyst (5 mol%) , $K_3PO_4$ (50 mol%), and $H_2O$ (500 mol%). However, these experiments were run

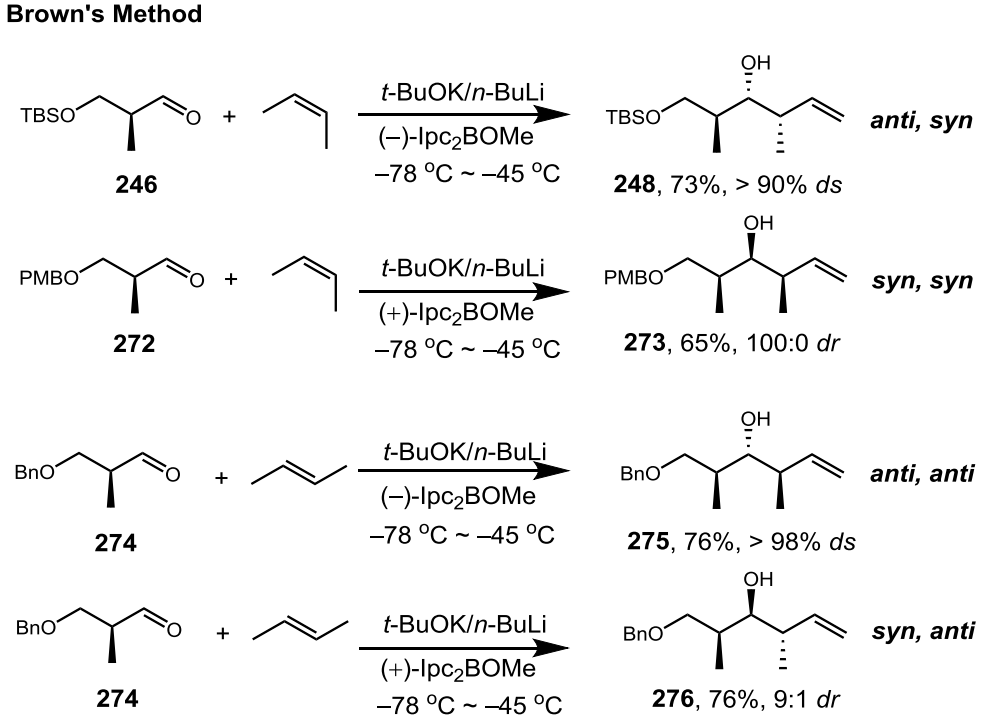
on a small scale (100 mg of alcohol **264**), and when we carried out the reaction on a larger scale (1.0 g of alcohol **264**) the yield dropped substantially (Scheme 2.16).

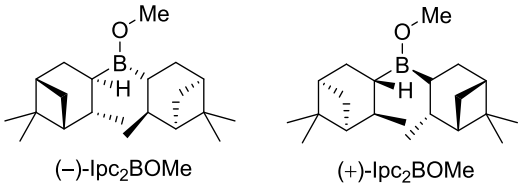



**Scheme 2.16.** Krische's crotylation reaction on large scale.

Considering that the reaction could not be scaled up, yields were moderate and long reaction times were required, we decided to discard this method for the synthesis of olefin **269** in favour of Brown's crotylation reaction.

### *2.2.1.2. Brown's Crotylation Reactions*



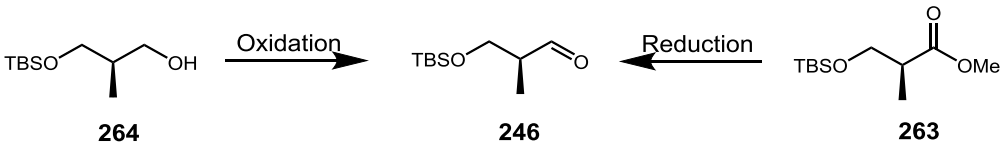



**Scheme 2.17** Synthesis of olefins with Brown's method.

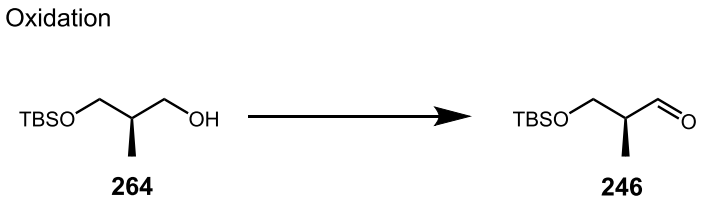
Brown's methodology has been extensively used in the synthesis of stereotriads in good yield and with moderate to excellent diastereoselectivity for all possible stereoisomers (Scheme 2.17).[160-162] Based on these precedents we decided to apply this methodology to the synthesis of our intermediate olefin.

To attempt Brown's crotylation, the corresponding aldehyde **246** was required. This compound can be prepared from the commercially available Roche ester using different strategies (Scheme 2.18A). As we had already prepared alcohol **263**, we studied the oxidation of this compound using different methods. Dess-Martin oxidation,[163a] Swern oxidation[163b] and Anelli's[163c] oxidation were tested, with the latter giving the best results (Scheme 2.18B). The reduction of ester **263** was also attempted, and it afforded the desired aldehyde **246** in excellent yield without purification on silica gel (Scheme 2.18C). To ensure that no epimerisation had occurred under the reduction conditions, the optical rotation was measured, and was found to match the previously reported data (Scheme 2.18C). Compared with the oxidation method, the reduction method is superior, as one less step is required.

A)

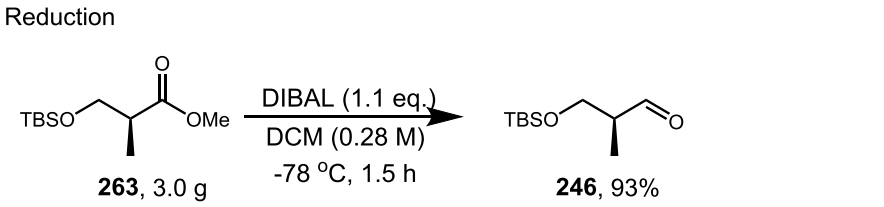



B)



| Entry | Oxidation Method | Reagents | Yield (%) |
|---|---|---|---|
| 1 | Dess-Martin | DMP | 60 |
| 2 | Swern | oxyl chloride, DMSO | 60 |
| 3 | Anelli | TEMPO, KBr, NaOCl | 86 |

C)

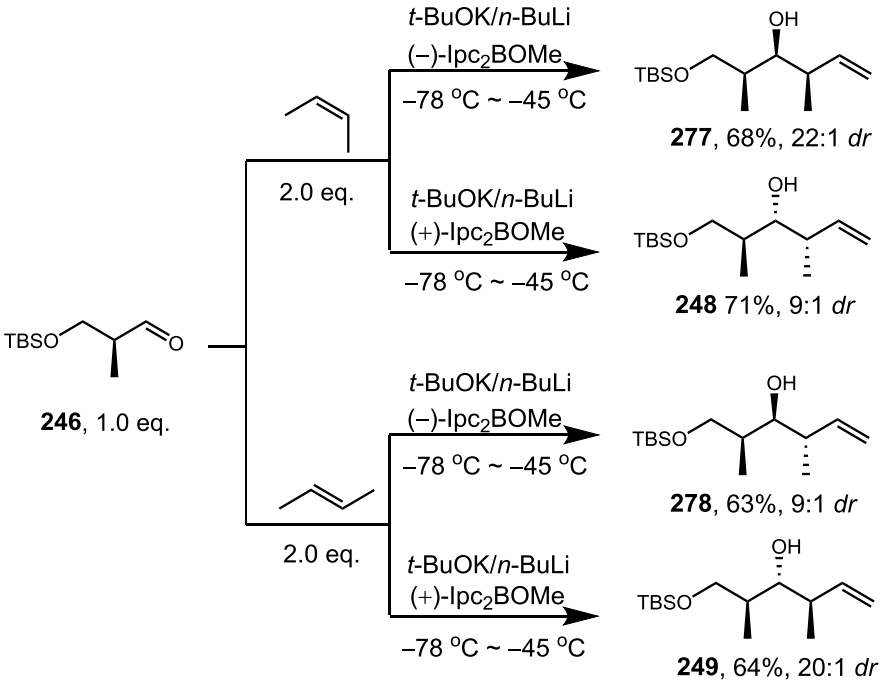



$[\alpha]_D^{20} = +33.1$

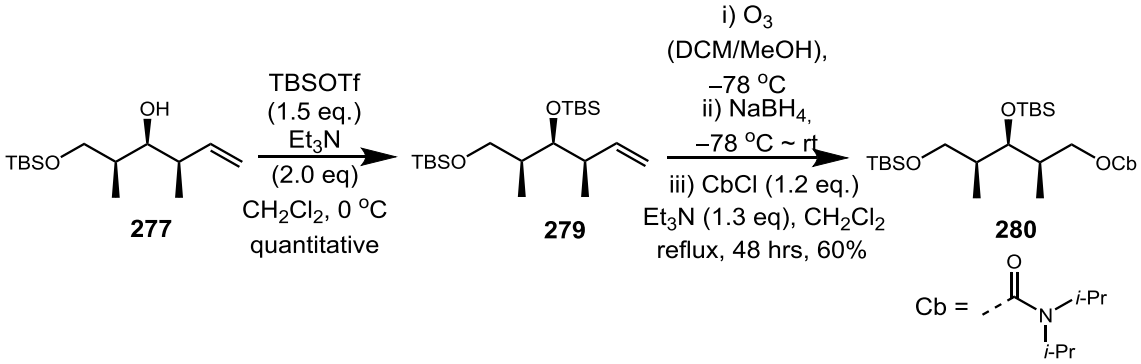
(Literature $[\alpha]_D^{20} = +32.5$)[164a]

**Scheme 2.18.** Synthesis of aldehyde **246**.

With aldehyde **246** in hand, four diastereoisomers of desired olefin (**248**, **249**, **277**, **278**) were synthesised using Brown's crotylation. All isomers were obtained in good yield and with high diastereoselectivity (Scheme 2.19). We then focused on the synthesis of the *syn-syn* diasteroisomer of the building blocks **A3**, we decided to prepare the alkyl *N*, *N*-diisopropyl carbamate as carbamates are known to be lithiated with a higher *er* value than the corresponding benzoate esters. Olefin **277** was thus submitted to TBS protection, ozonolysis and carbamoylation, to afford carbamate **280** in good yield (overall yield: 60%, Scheme 2.20).

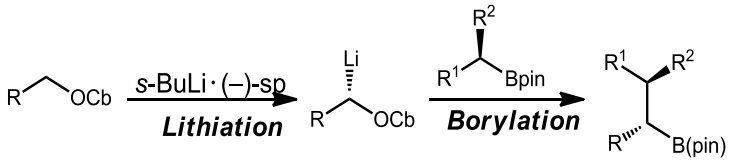



**Scheme 2.19.** Preparation of olefin **248**-**249** & **277**-**278** with Brown's crotylation,




**Scheme 2.20.** Preparation of alkyl *N*,*N*-diisopropyl carbamate **280**.

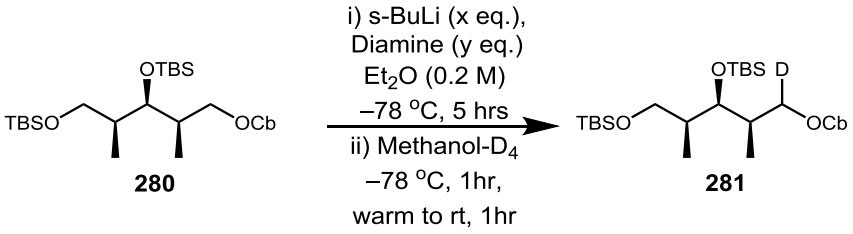
### *2.2.1.3. Lithiation–Deuteration Studies of Alkyl N, N-Diisopropyl Carbamate*




**Scheme 2.21.** Lithiation–borylation reaction.

With carbamate **280** in hand, we sought to apply this building block to the lithiation–borylation reaction (Scheme 2.21). Firstly, we started probing the efficiency of the lithiation step by trapping the lithiated species with $CD_3OD$ and determining the deuterium incorporation by $^1H$ NMR spectroscopy. The initial effort using a combination of 1.5 equivalents of *s*-BuLi and the achiral diamine TMEDA resulted in only 36% deuterium incorporation (Entry 1, Table 2.4). With a great increase in the amount of base and diamine (3.0 equivalents), full deuterium incorporation was observed indicating that complete lithiation was achieved (Entry 2, Table 2.4). However, if the lithiation–borylation reaction was conducted under these conditions (3 equivalents of *s*-BuLi), a large amount of boronic ester (3 equivalents) will be required, which is an issue when valuable boronic esters are utilised. We therefore continued the investigation with less base and utilised the chiral diamine (+)-sparteine, which will ultimately be employed in this asymmetric project in place of TMEDA. Unfortunately, a drastic decrease in deuterium incorporation was observed (Entry 3 and 4, Table 2.4).

**Table 2.4.** Lithiation–deuteration reaction on carbamate **280**[a].




| Entry | *s*-BuLi (eq.) | Diamine | Diamine (eq.) | D (%) |
|---|---|---|---|---|
| 1 | 1.5 | TMEDA | 1.5 | 36 |
| 2 | 3.0 | TMEDA | 3.0 | 100 |
| 3 | 2.0 | (+)-sp | 2.0 | 35 |
| 4 | 2.5 | (+)-sp | 2.5 | 55 |

[a.] Carbamate **280** (40 mg), conversion was determined by $^1H$ NMR.

### 2.2.2. Preparation and Lithiation–Deuteration Studies of Alkyl Benzoate Esters

Due to the difficult lithiation of carbamate **280**, we decided to utilise the corresponding triisopropyl benzoate ester to seek a higher efficiency in lithiation (Figure 2.5). Meanwhile we were determined to screen the effect of different protecting groups of the secondary hydroxyl group. In addition, we also decided to change the terminal protecting group to achieve a more efficient protecting group strategy in later stages of the project.


**Figure 2.5.** Alkyl triisopropyl benzoate ester for lithiation-deuteration.

#### *2.2.2.1. Preparation of Alkyl Benzoate Esters*

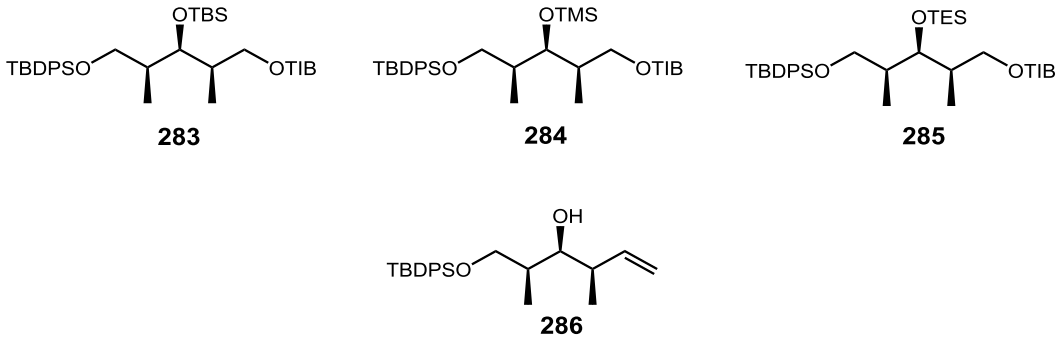
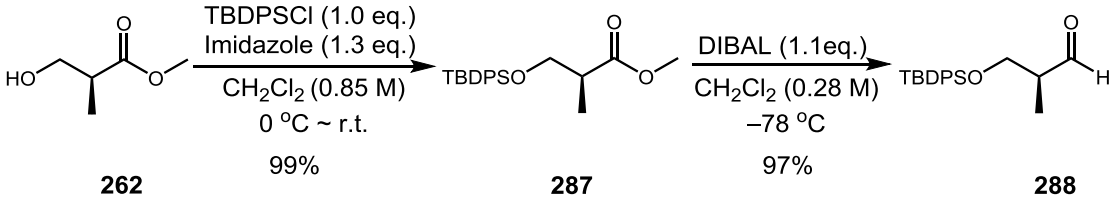
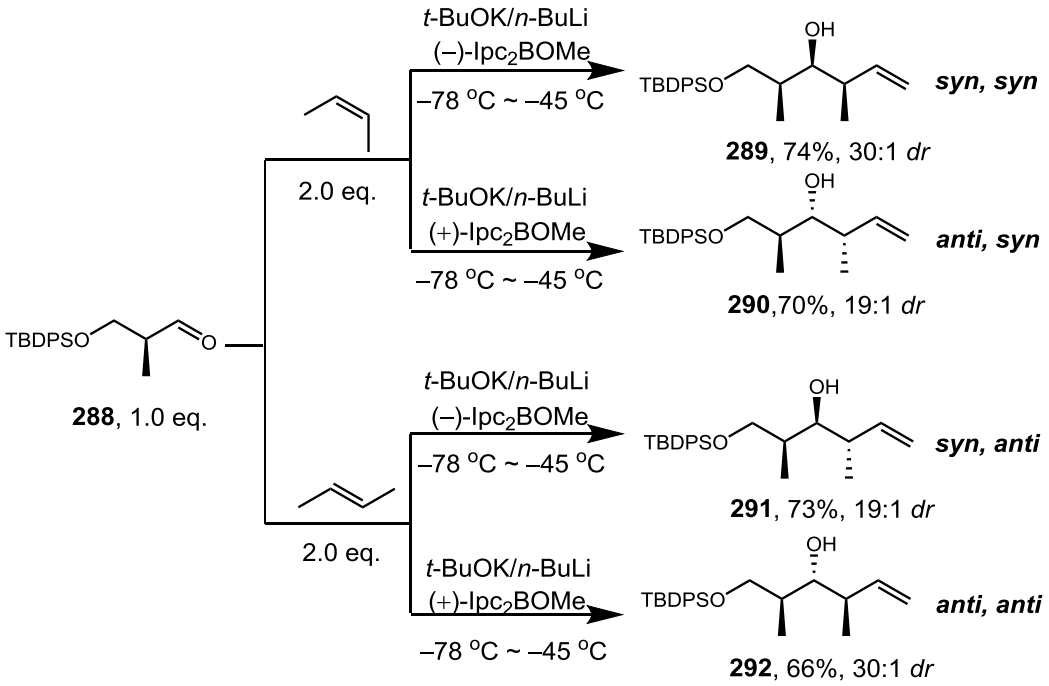



**Figure 2.6.** Alkyl benzoate esters for lithiation–deuteration.

As discussed above, we embarked on the exploration with the synthesis of benzoate ester **283-285** (Figure 2.6) that can be accessed from olefin **286** (Figure 2.6) via ozonolysis, Mitsunobu reaction and protection. Firstly, aldehyde **288** was synthesised via protection and reduction reactions in excellent yields (Scheme 2.22), starting from the (*S*)-Roche ester **262**. Subsequently, olefin **289** and three other stereoisomers **290-292** were prepared using Brown's crotylation reaction with all isomers obtained in high yield and excellent diastereoselectivity (Scheme 2.23).

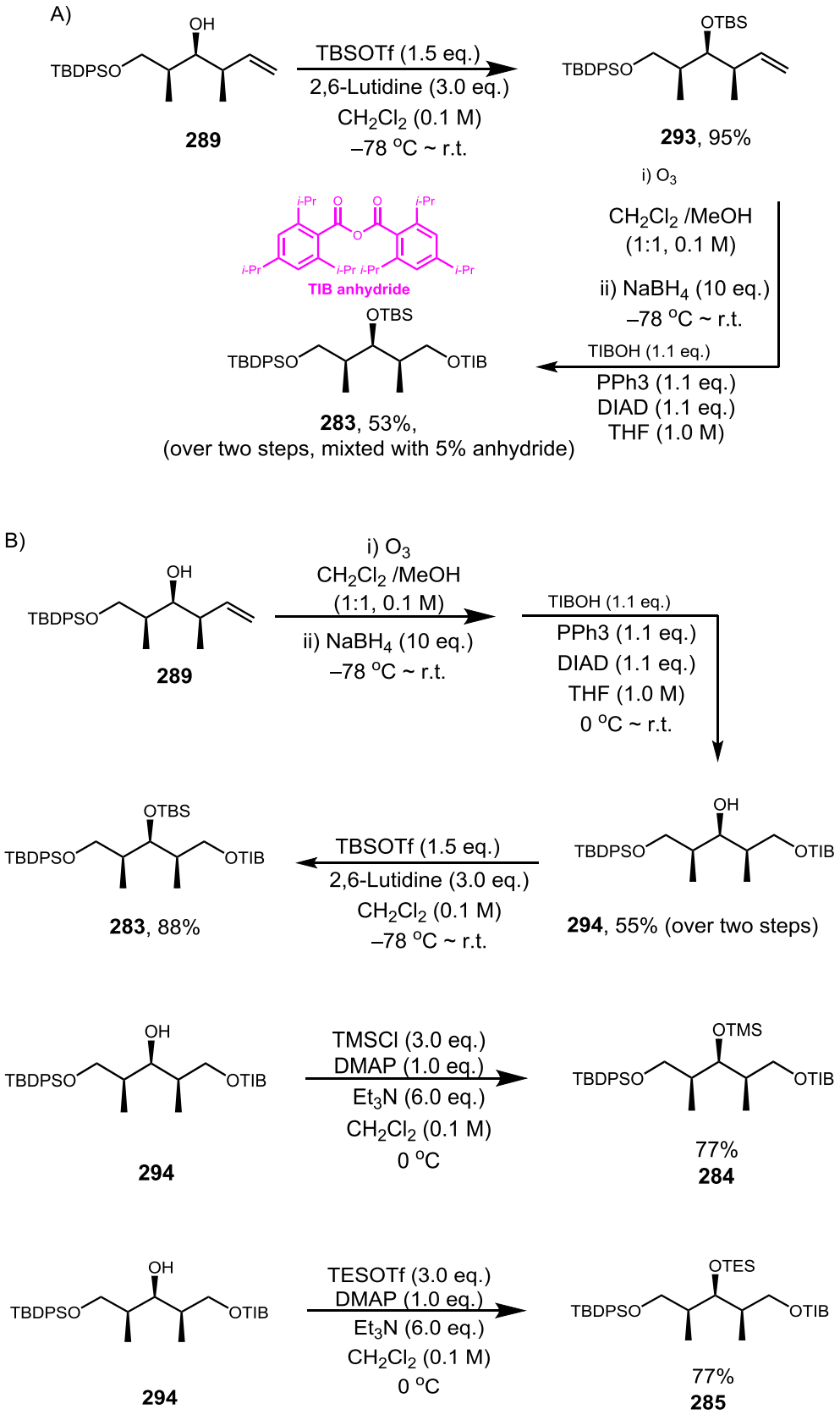



**Scheme 2.22.** Preparation of aldehyde **288**.




**Scheme 2.23.** Preparation of olefin **289**-**292**.

With olefin **289** in hand, we carried out the synthesis of benzoate ester **283**. It could be prepared following two different strategies. Firstly, **289** can be protected, and then subjected ozonolysis and a Mitsunobu reaction to yield benzoate ester **283** (Scheme 2.24A). However, a side product, TIB anhydride, was produced from the Mitsunobu reaction (Scheme 2.24A), which possessed an extremely similar $R_f$ value with benzoate ester **283**, and thus efficient purification of benzoate ester **283** via this route is very difficult.



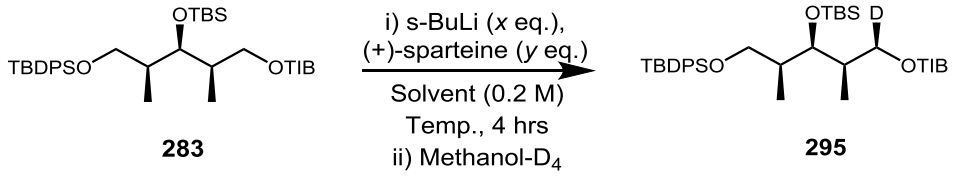

**Scheme 2.24.** Preparation of benzoate esters **283, 284** & **285**.

As a result, we turned to an alternative protocol, in which the ozonolysis and Mitsunobu reactions were conducted first, followed by the protection of benzoate ester **294** to afford benzoate ester **283**; the aforementioned TIB anhydride could be isolated in this case, and pure benzoate ester **283** was thus obtained in high yield (Scheme 2.24B). Benzoate esters **284** & **285** were also prepared successfully in good yields utilising the same strategy (Scheme 2.24B).

#### *2.2.2.2. Lithiation–Deuteration Studies on Alkyl Benzoate Esters*

With the alkyl benzoate esters successfully prepared, the lithiation–deuteration reactions were investigated. The investigation was firstly carried out with benzoate ester **283** by optimising the amount of base, solvent and temperature. Employment of 3.0 equivalents of base and TMEDA afforded nearly completely deuterated benzoate ester **295** (Entry 4, Table 2.5). However, when (+)-sparteine was employed as the ligand, the D-incorporation was decreased to 76%, which may result from the increased steric demand of (+)-sparteine (Entry 3, Table 2.5). Decrease in D–incorporation was also observed when the amount of base was reduced (Entry 1 and 2, Table 2.5). Additionally, the diastereoselectivity is not very good, with *d.r.* values of around 4:1 (Entry 1-4, Table 2.5). Elevated temperature (–60 $^{o}$C) gave higher D-incorporation yields, but the *d.r.* values were slightly lower (Entry 1 and 5, Table 2.5). The decrease in diastereoselectivity was likely caused by the instability of the carbanion at a higher temperature. The amount of diamine was screened, as it was previously discovered that an excess of diamine can enhance the lithiation within the group. However, increasing the amount of diamine did not improve the reaction (Entry 5-7, Table 2.5). Different solvents (CPME, toluene) were also examined, unfortunately, none of them could afford a better result (Entry 8-9, Table 2.5). With benzoate ester **283**, satisfactory lithiation cannot be achieved, although the results are better compared with those of alkyl carbamate **280** (Table 2.4).

**Table 2.5.** Lithiation–deuteration reaction on benzoate ester **283** [a].




| Entry | Solvent | Temp. (°C) | Base/sp (eq.) | D (%) | *d.r.* |
|---|---|---|---|---|---|
| 1 | $Et_2O$ | –78 | 2.0/2.0 | 68 | 80:20 |
| 2 | $Et_2O$ | –78 | 2.5/2.5 | 75 | 81:19 |
| 3 | $Et_2O$ | –78 | 3.0/3.0 | 76 | 79:21 |
| 4 | $Et_2O$ | –78 | 3.0/3.0 (TMEDA) | 92 | 63:37 |
| 5 | $Et_2O$ | –60 | 2.0/2.0 | 87 | 77:23 |
| 6 | $Et_2O$ | –60 | 2.0/6.0 | 85 | 75:25 |
| 7 | $Et_2O$ | –60 | 1.6/6.0 | 87 | 74:24 |
| 8 | CPME | –78 | 2.0/2.0 | 52 | 75:25 |
| 9 | Toluene | –78 | 2.0/2.0 | 10 | 80:20 |

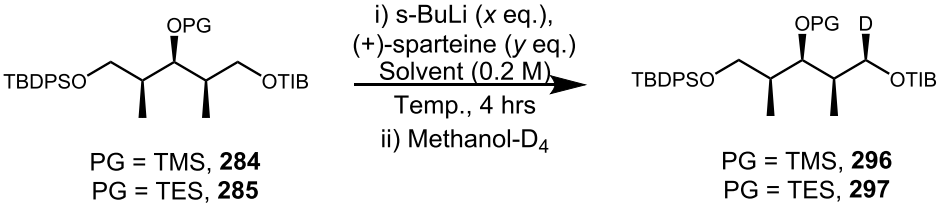
[a.] Benzoate ester **283** (50 mg), yield was determined by $^1$H NMR.

As the TBS group is a sterically bulky protecting group, it can hinder the lithiation of benzoate ester **283**. Less sterically hindered benzoate esters may provide better results. We therefore continued to examine lithiation–deuteration efficiency utilising benzoate esters **284** & **285** (Table 2.6) with TMS or TES protecting groups.

The exploration was first conducted with benzoate ester **284**, which was treated with *s*-BuLi and (+)-sparteine at –78 °C and trapped with $CD_3OD$. As a large excess of base was not desirable, 2.0 equivalents or less were utilised in the reactions (Entry 1-4, Table 2.6). Screening of base equivalents and solvents did not greatly improve the D-incorporation, or diastereoselectivity, which ranges from 76:24 to 86:14 (Entry 1-4, Table 2.6). Furthermore, some deprotected product was observed, which indicated that the TMS group was not stable under lithiation conditions. As a result, we did not continue the exploration with benzoate ester **284**. Comparatively, benzoate ester **285** is more stable than benzoate ester **284**, but not as bulky as benzoate ester **283**. Thus, the lithiation efficiency was further examined using benzoate ester **285**. The

compound was tested in various solvents (ether solvent and toluene) in the presence of 2.0 equivalents of base and (+)-sparteine. However, no obvious improvement could be achieved in comparation with the cases of benzoate ester **283** (Entry 5-8, Table 2.6), which indicates the decrease in steric hindrance had minimal effect.

**Table 2.6:** Lithiation–deuteration reaction on benzoate **284** & **285**.[a]




PG = TMS, **284**
PG = TES, **285**

PG = TMS, **296**
PG = TES, **297**

| Entry | PG | Solvent | Temp. (°C) | Base/sp (eq.) | D (%) | *d.r.* |
|---|---|---|---|---|---|---|
| 1 | TMS | $Et_2O$ | −78 | 1.5/1.5 | 65 | 80:20 |
| 2 | TMS | $Et_2O$ | −78 | 2.0/2.0 | 78 | 86:14 |
| 3 | TMS | TBME | −78 | 2.0/2.0 | 68 | 80:20 |
| 4 | TMS | CPME | −78 | 2.0/2.0 | 67 | 76:24 |
| 5 | TES | $Et_2O$ | −78 | 2.0/2.0 | 78 | 86:14 |
| 6 | TES | $Et_2O$ | −78 | 2.0/2.0 | 78 | 86:14 |
| 7 | TES | CPME | −78 | 2.0/2.0 | 64 | 77:23 |
| 8 | TES | Toluene | −78 | 2.0/2.0 | 20 | 85:15 |

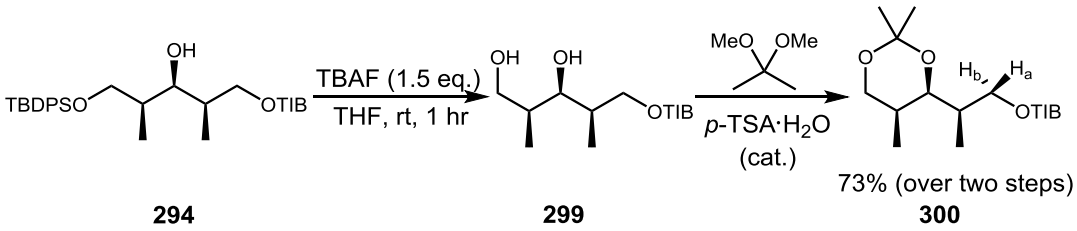
[a] Benzoate ester **284** or **285** (50 mg), yield (D%) was determined by $^1$H NMR.

Based on the above investigation, we can conclude that benzoate esters with silyl protecting groups are difficult to deprotonate as they display poor D-incorporation and poor diastereoselectivity. The large steric hindrance of these compounds is predicted to be the main factor contributing to this difficulty.

### 2.2.3. Preparation and Lithiation–Deuteration of Cyclic Benzoate Esters

#### *2.2.3.1. Lithiation–Deuteration Studies on Cyclic Benzoate Esters*

We have reasoned that to solve the problem of lithiation, a less hindered benzoate ester should be employed. One possible solution is to protect the secondary hydroxyl group with a smaller protecting group. The other solution is to prepare benzoate esters with the 1,3-diol protected as an acetal group (e.g., benzoate esters **300**, Scheme 2.25), which can effectively reduce the steric hindrance. Therefore, we first synthesised benzoate ester **300** in good yield (Scheme 2.25) by deprotection of benzoate ester **294** and the subsequent protection of diol **299**. Benzoate ester **300** was then subjected to lithiation–deuteration investigations.




**Scheme 2.25.** Preparation of benzoate ester **300**.

Gratifyingly, benzoate ester **300** showed much better reactivity towards lithiation and was completely lithiated utilising 2.0 equivalents of base with (+)-sparteine as ligand (Figure 2.7). Normally, the $H_a$ should be deprotonated when employing (+)-sparteine as ligand. However, the main product (compound **301a**) was the diastereomer of the expected product based on reagent control, with a *d.r.* value of around 3:1 in this case. It can be explained by the coordination of the oxygen atom of the acetonide to the lithium cation in the benzoate ester **300** that enhances the substrate control effect (Figure 2.7A). Hoppe and co-workers reported a similar example in 1995 but with 5 membered oxazolidine carbamates (Cby) (Figure 2.7B).[165] Returning to substrate **300**, according to the proposed models for lithiation (Figure 2.7C and D), the proton $H_b$ would be easily deprotonated. When (–)-sparteine was employed, it was a matched case and good stereoselectivity was achieved (Figure 2.7C); however, a mismatched case would arise when employing (+)-sparteine as ligand due to the steric interaction between the ligand

and acetonide group, so the diastereoselectivity was not very high (Figure 2.7D). However, the major stereoisomer resulted from removal of the $H_b$ proton, the same with the case when utilising (–)-sparteine.

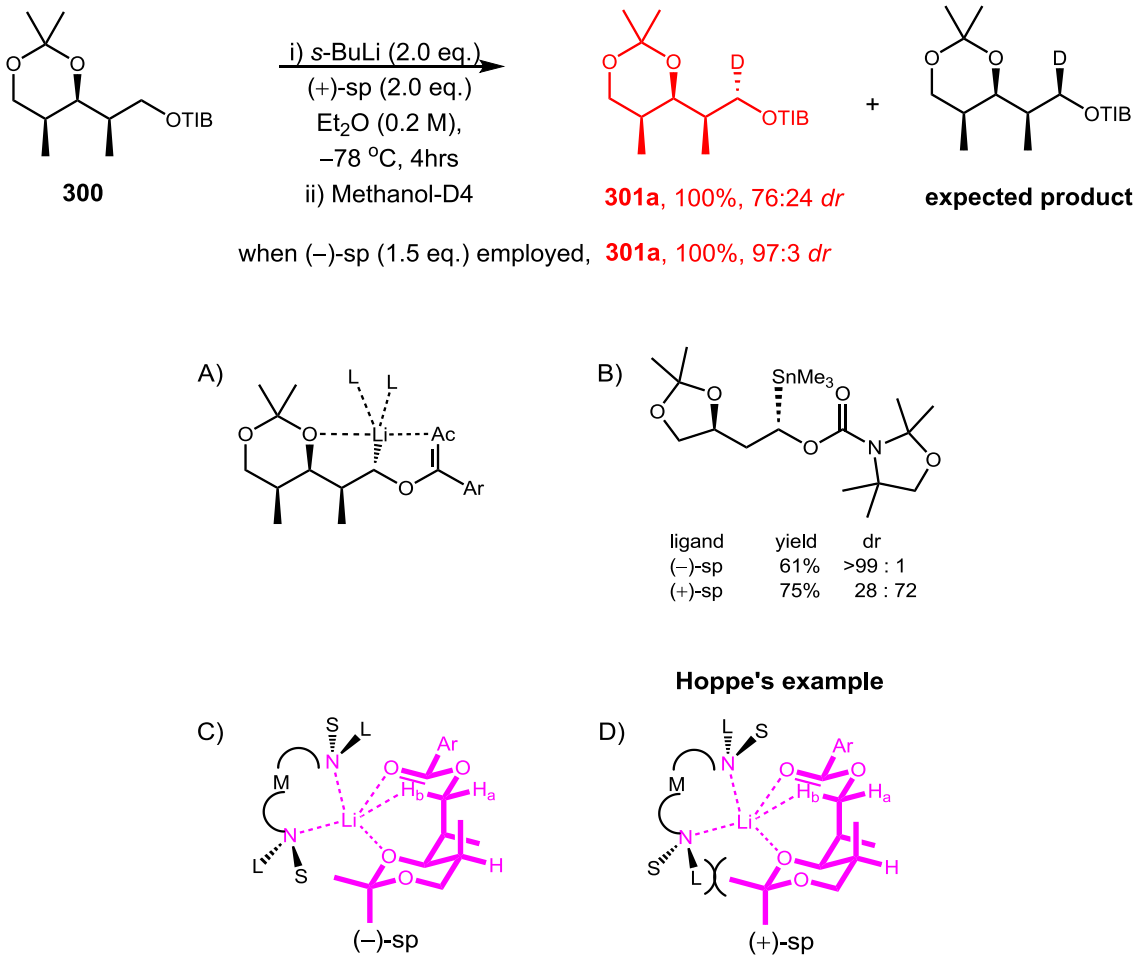
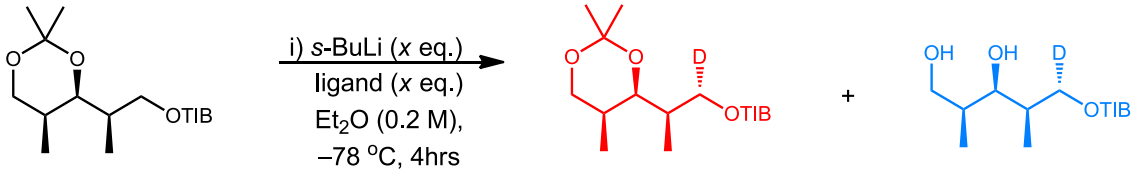



**Figure 2.7.** Coordination of benzoate ester **300** to lithium.

In addition to compound **301a**, a ring-opened product compound **301b** was also detected (Entry 1, Table 2.7). The ratio between compounds **301a** and **301b** was roughly 1:1. When less base was employed, less ring-opened product was formed (Entry1, 2 and 4, Table 2.7). When the reaction time was reduced, a decrease in the formation of compound **301b** was observed as well (Entry 4 and 6, Table 2.7). Lithiation–deuteration reactions employing (–)-sparteine as ligand were also examined. In accordance with expectation, these cases were matched cases, and completely deuterated compound **301a** was produced with excellent diastereoselectivity (Entry 3 and 5, Table 2.7). Less ring-opened compound **301b** was also detected when 1.5

equivalents of base were employed in the presence of (–)-sparteine (Entry 3, Table 2.7). Compound **301b** was not formed when 1.2 equivalents of base were utilised (Entry 5, Table 2.7). Various solvents (Entry 8-10, Table 2.7) were investigated to determine the impact on the D-incorporation and diastereoselectivity. However, the undesired isomer **301a** was still the main product in THF or $Et_2O$ (Entry 9-10, Table 2.7). The *d.r.* was around 1:1 in toluene, but the D-incorporation was drastically decreased to only 16% (Entry 10, Table 2.7).

**Table 2.7.** Lithiation–deuteration reaction of benzoate ester **300**[a].

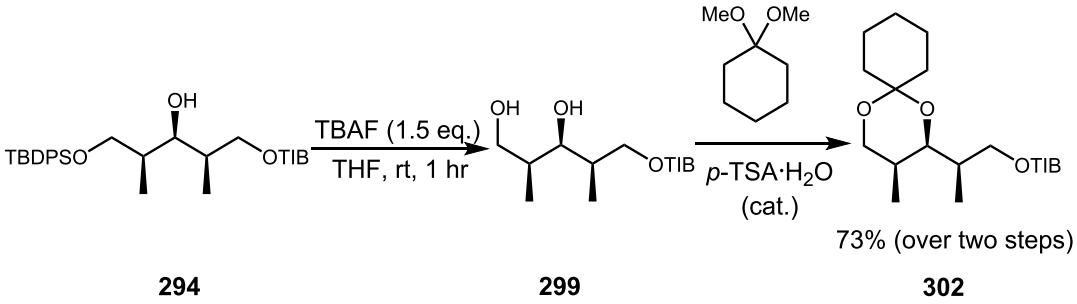



**300** **301a** **301b**

| | Base/ligand (x eq.) | Ligand | 301a D% (a) | 301a *d.r.* | 301b D%(b) | 301b *d.r.* | 301a: 301b |
|---|---|---|---|---|---|---|---|
| **1** | 2.0 | (+)-sp | **100** | **76:24** | 91 | 88:12 | 55:45 |
| **2** | 1.5 | (+)-sp | **85** | **77:23** | 90 | 81:19 | 66:34 |
| **3** | 1.5 | (–)-sp | **100** | **97:3** | 100 | 98:2 | 85:15 |
| **4** | 1.2 | (+)-sp | **93** | **82:18** | 94 | 79:21 | 86:14 |
| **5** | 1.2 | (–)-sp | **100** | **95:5** | -- | -- | -- |
| **6** | 1.2 | (+)-sp | **100(1h)** | **67:33**[b] | | | 90:10 |
| **7** | 1.2 | TMEDA | **99** | **89:11** | 100 | 90:10 | 48:52 |
| **8** | 1.2 | none | **80** | **91:9** | -- | -- | -- |
| **9** | 1.2 | none | **98** | **66:34**[c] | | | 57:43 |
| **10** | 1.2 | none | **16** | **43:57**[d] | -- | -- | -- |

[a.] Benzoate ester **300** (50 mg), D% was determined by $^1$H NMR of crude reaction mixture;
[b.] lithiation time is 1 hr, dr is a mixture result of **301a** and **301b**; [c.] THF was used as solvent;
[d.] toluene was used as solvent.

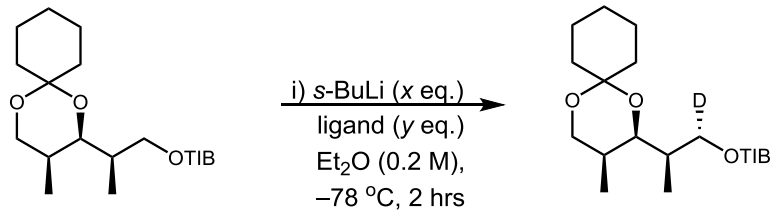
In conclusion, benzoate ester **300** can undergo efficient lithiation, with (–)-sparteine or TMEDA as ligand and excellent diastereoselectivity can be achieved. It is noteworthy that the reaction is strongly substrate-controlled, and the expected isomer could not be obtained in (+)-sparteine cases.




**294** **299** **302**

**Scheme 2.26.** Preparation of benzoate ester **302**.

**Table 2.8:** Lithiation–deuteration reaction on benzoate ester **302**[a].



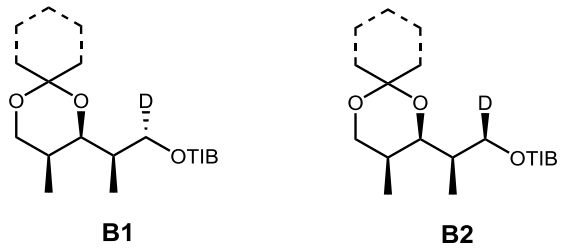

**302** **303**

| Entry | *s*-BuLi/ligand (eq.) | Ligand | D% (a) | *d.r.* |
|---|---|---|---|---|
| **1** | 1.2 | (+)-sp | 87[b] | 74:26 |
| **2** | 1.2 | (+)-sp | 98 | 76:24 |
| **3** | 1.2 | TMEDA | 98 | 92:8 |
| **4** | 1.2 | (–)-sp | 99 | 98:2 |
| **5** | 1.2 | none | 74 | 93:7 |
| **6** | 1.2 | none | 100[c] | 68:32 |

[a.] Benzoate ester **300** (50 mg), yield was determined by $^1$H NMR; [b.] the time for lithiation was 1.0 hour; [c.] THF was used as the solvent.

Later, we probed the lithiation–deuteration on benzoate ester **302** (Scheme 2.26), which was expected to be more stable than benzoate ester **300**, and thus avoid the ring-opening problem. As shown in Table 2.8, no ring-opened product was detected when **302** was treated with *s*-BuLi and (+)-sparteine (Entry 1-5, Table 2.8). However, as observed with benzoate ester **300**, the same diastereoisomer was obtained as the major product when either enantiomer of sparteine was used, showing strong substrate control (Entry 1-2, Table 2.8). Also, excellent *d.r.* could be achieved when TMEDA was utilised (Entry 3, Table 2.8), which is beneficial as TMEDA is both less steric hindered and less costly than sparteine. Excellent diastereoselectivity was obtained in the absence of diamine ligand, with a decrease in D-incorporation (Entry 5, Table 2.8). When the reaction was conducted in THF, comparable results were obtained to benzoate ester **300** (Entry 6, Table 2.8).

To conclude, both benzoate ester **300** and **302** underwent efficient lithiation in excellent yields and diastereoselectivity–although this selectivity is controlled by the substrate. Benzoate ester **302** is more stable than benzoate ester **300**. Additionally, compound **B1** (isomer **B1**, Figure 2.8) was the major product in all cases no matter which diamine was employed.



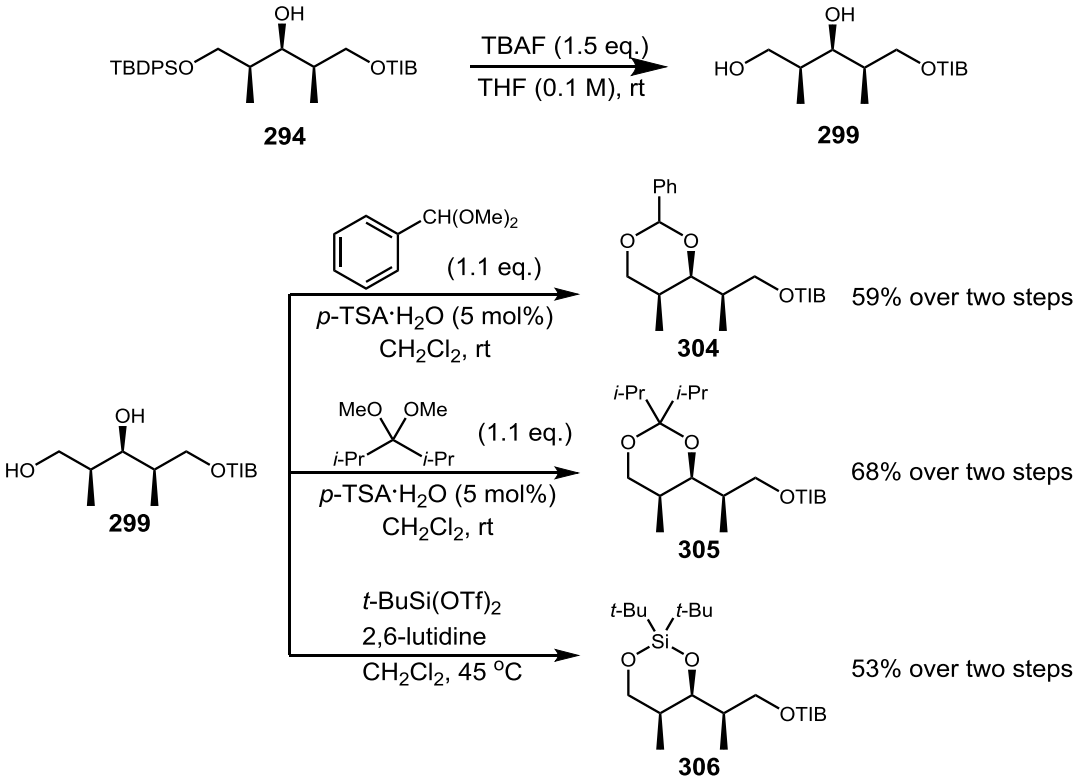

**B1** **B2**

**Figure 2.8.** Deuterated stereoisomers of benzoate ester **300** and **302**.

### *2.2.3.2.* Further Explorations of Cyclic Benzoate Esters with Various Protecting groups

To address the issue of substrate control dominating over reagent control, we decided to screen some other protecting groups. Firstly, we prepared benzoate esters **304-306** starting from benzoate ester **294**, which underwent deprotection of primary hydroxyl group, and was followed by protection of diol **299** with different acetals affording the

corresponding product in moderate yields, 59%, 68% and 53% respectively (**Scheme 2.27**).

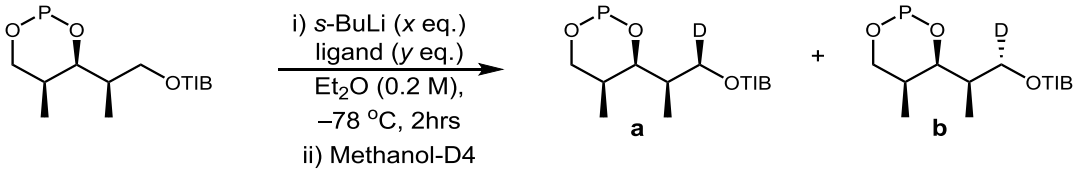



**Scheme 2.27.** Synthesis of benzoate ester **304-306**.

With these benzoate esters in hand, the lithiation–deuteration reactions were conducted (Table 2.9). Firstly, benzoate ester **304** was lithiated using (+)-sparteine as ligand, and complete deuteration was observed after being trapped by $CD_3OD$; however, the same substrate control effect was detected (Entry 1, Table 2.9). Subsequently, the more hindered benzoate ester **305** was examined, which also gave similar results (Entry 2, Table 2.9). As similar substrate control was observed, we did not test the lithiation–deuteration reaction using TMEDA or (–)-sparteine as ligand in the cases of benzoate esters **304** and **305**. Furthermore, the lithiation–deuteration reactions were investigated using benzoate ester **306**. It is relatively bulkier compared with benzoate ester **304** and **305**. Thus, longer reaction time (Entry 4, Table 2.9) or larger amount of base (Entry 5, Table 2.9) would probably be required. We therefore carried out the reactions under various conditions, and it was discovered that benzoate ester **306** was completely deuterated with a *d.r.* of 50:50 (Entry 3-5, Table 2.9). Although the substrate control

effect was not avoided, this result is still valuable to the project, as it provides an opportunity to isolate the two isomers (**307** and **308**, **Scheme 2.27**) if the lithiated benzoate ester **306** is trapped by $Me_3SnCl$. To further probe the property of benzoate ester **306**, different ligands were screened. As anticipated, using (–)-sparteine or TMEDA gave isomer **b** as the major product in excellent yield and diastereoselectivity (Entry 6-7, Table 2.9). When the reaction was conducted in the absence of ligand, substrate control was also observed (Entry 8, Table 2.9).

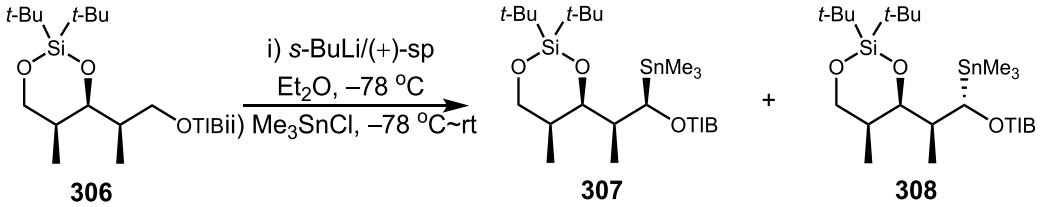
**Table 2.9.** Lithiation–deuteration reactions on benzoate **304** to **306**.




| Entry | Benzoate | P | Base/ligand (eq.) | Ligand | D% [a] | *d.r.* (a:b) |
|---|---|---|---|---|---|---|
| 1 | **304** | -(Ph)CH- | 1.2 | (+)-sp | 100 | 19:81 |
| 2 | **305** | -($i$-Pr)$_2$C- | 1.2 | (+)-sp | 100 | 31:69 |
| 3 | **306** | -($i$-Bu)$_2$Si- | 1.2 | (+)-sp | 100 | 50:50 |
| 4 | **306** | -($i$-Bu)$_2$Si- | 1.2 | (+)-sp | 100(5h) | 50:50 |
| 5 | **306** | -($i$-Bu)$_2$Si- | 2.0 | (+)-sp | 100 | 50:50 |
| 6 | **306** | -($i$-Bu)$_2$Si- | 1.2 | (–)-sp | 100 | 5:95 |
| 7 | **306** | -($i$-Bu)$_2$Si- | 1.2 | TMEDA | 100 | 14:86 |
| 8 | **306** | -($i$-Bu)$_2$Si- | 1.2 | none | 67 | 61:39 |

*a.* Determined by $^1$H MNR of crude reaction mixture.

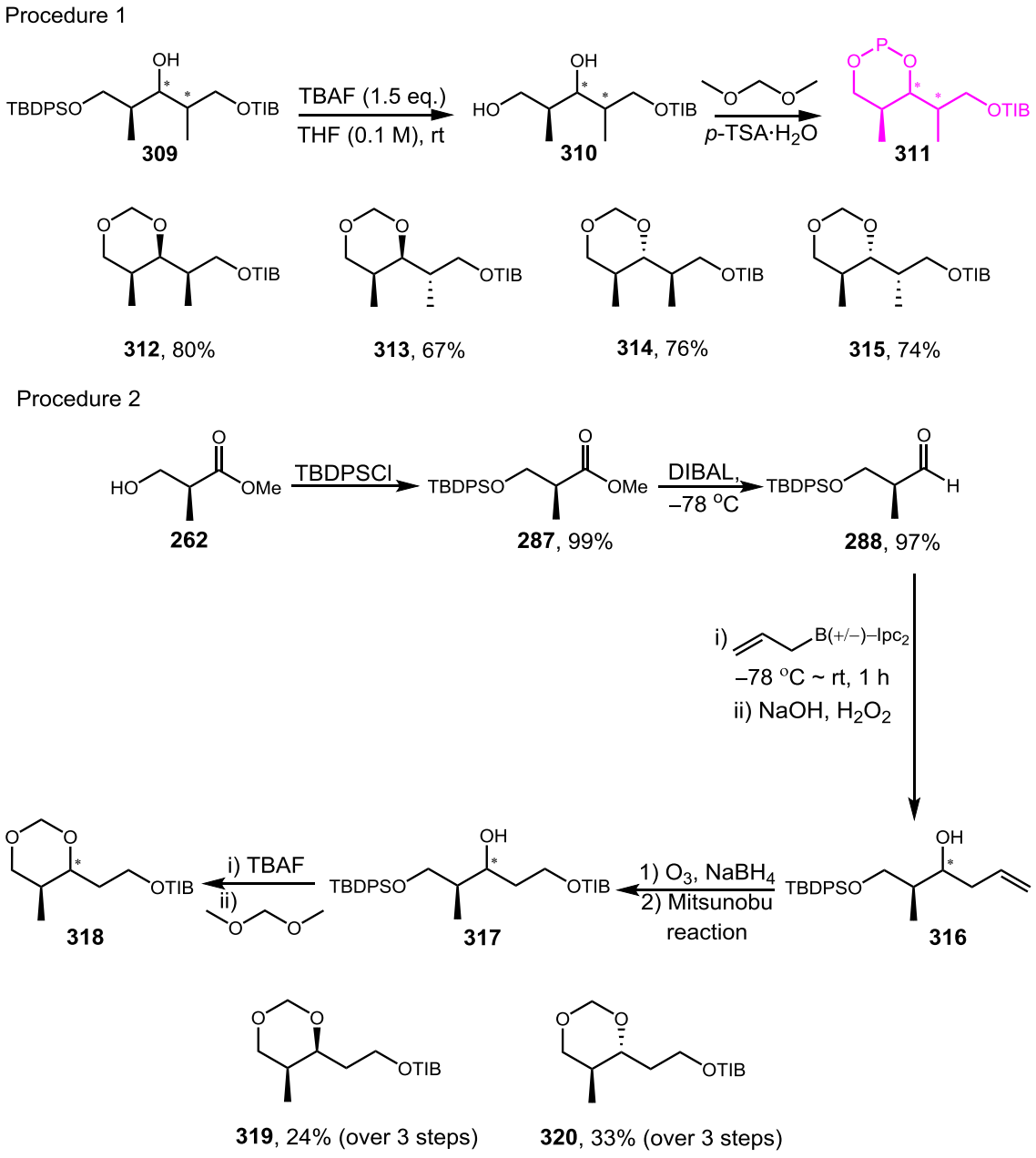
*b.*




**Scheme 2.28.** Proposed preparation of stannanes using lithiated benzoate **306**.

### 2.2.4. Study on the Substrate Control Effect of Polypropionate Stereotriads

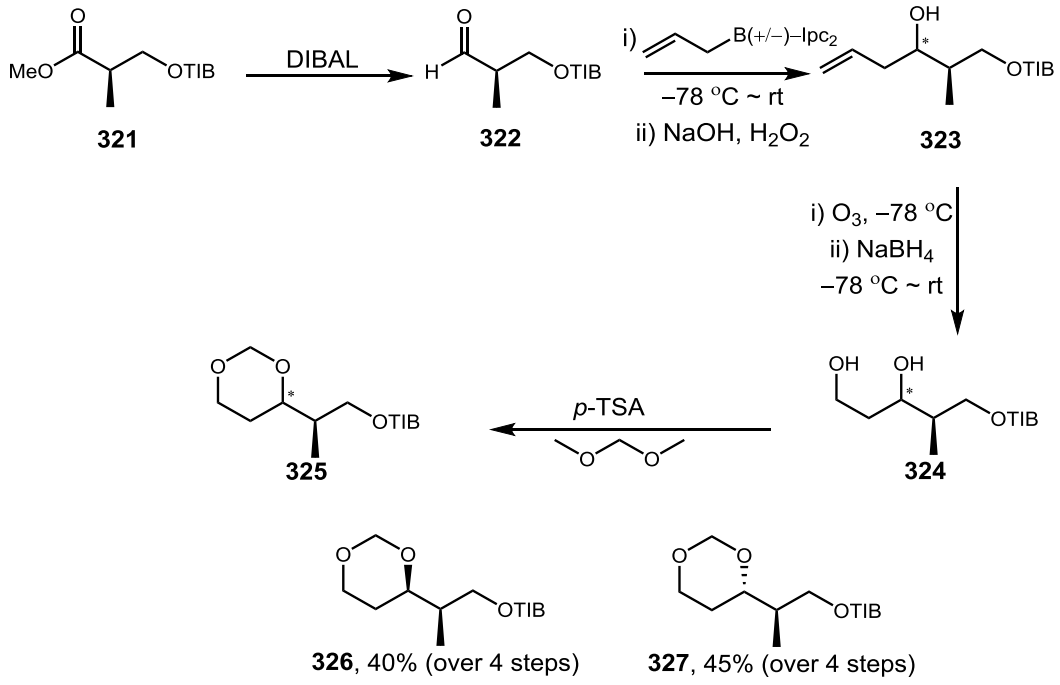
The substrate effect always existed despite variation of protecting groups. Nevertheless, we embarked on a study of the effects of the following factors on the stereochemistry of lithiation: protecting groups (PG), stereochemistry of substituents, and positions of substituents.




**Scheme 2.29.** Synthesis of benzoate esters **312**-**315** & **319**-**320**.

Firstly, all the necessary stereotriad building blocks were synthesised. To avoid the steric hindrance of protecting groups when studying the effect of stereochemistry and methyl positions, we decided to prepare some less hindered benzoate esters. Consequently, benzoate esters **312** to **315** were prepared in moderate yields via deprotection of benzoate ester **309** and following protection of diol **310** with dimethoxymethane (Scheme 2.29). Benzoate esters **319** and **320** were produced by procedure 2 (Scheme 2.29), with an allylation reaction instead of crotylation reaction. Benzoate esters **326** and **327** were synthesised via procedure 3, which was similar to procedure 2 but employed different starting materials (Scheme 2.30).

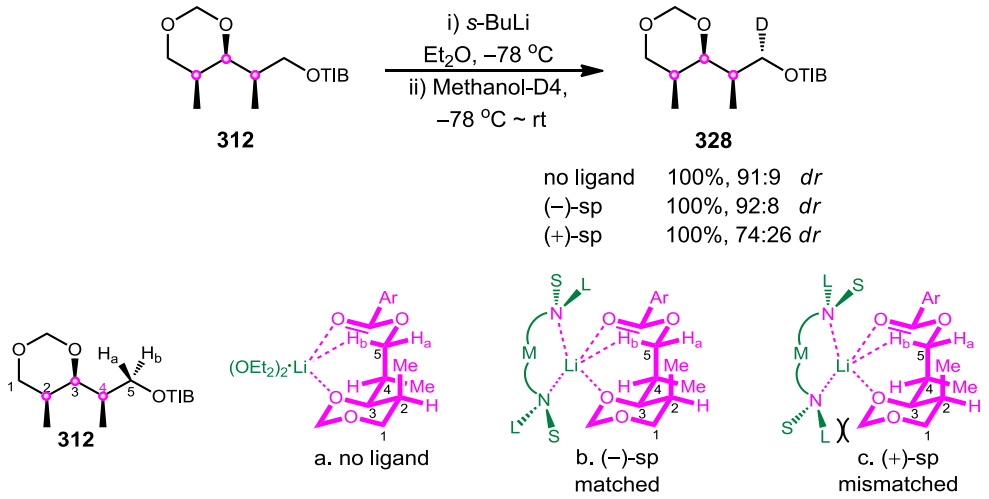
Procedure 3




**Scheme 2.30.** Synthesis of benzoate esters **326** and **327**.

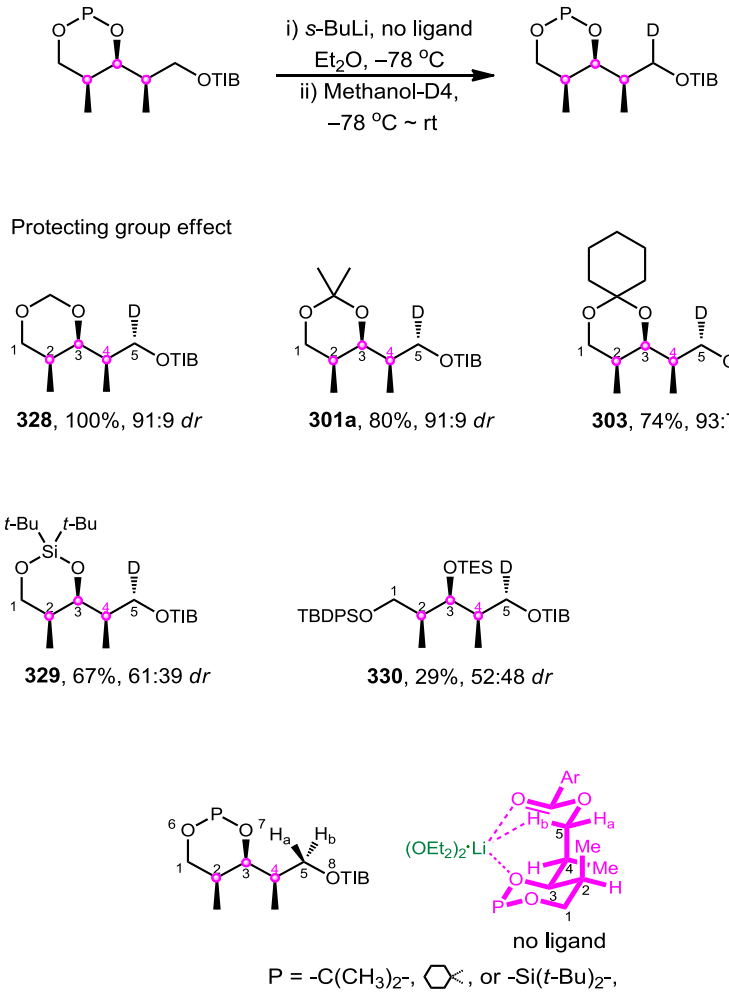
The study was initiated with benzoate ester **312**, which was deprotonated by *s*-BuLi in the absence of any additive ligand and trapped with $CD_3OD$ at –78 °C. Strong substrate control was observed with benzoate ester **312** under these conditions. Complete lithiation and high diastereoselectivity (91:9) were achieved (no ligand, Scheme 2.31). The ratio was slightly increased in the presence of (–)-sparteine, while the addition of (+)-sparteine led to a lower ratio but still of the '(–)-sparteine' directed diastereoisomer (Scheme 2.31). The selectivity can be explained by conformation **a**-**c** (Scheme 2.31), in

which the steric interaction between 2-methyl group and 4-methyl group can be avoided. In the presence of (–)-sparteine, a matched case can arise, as a result a higher *d.r.* value was obtained; while in the case of (+)-sparteine, there was an interaction between the large substituent of (+)-sparteine and the 6-membered ring, resulting in a lower *d.r.* value.



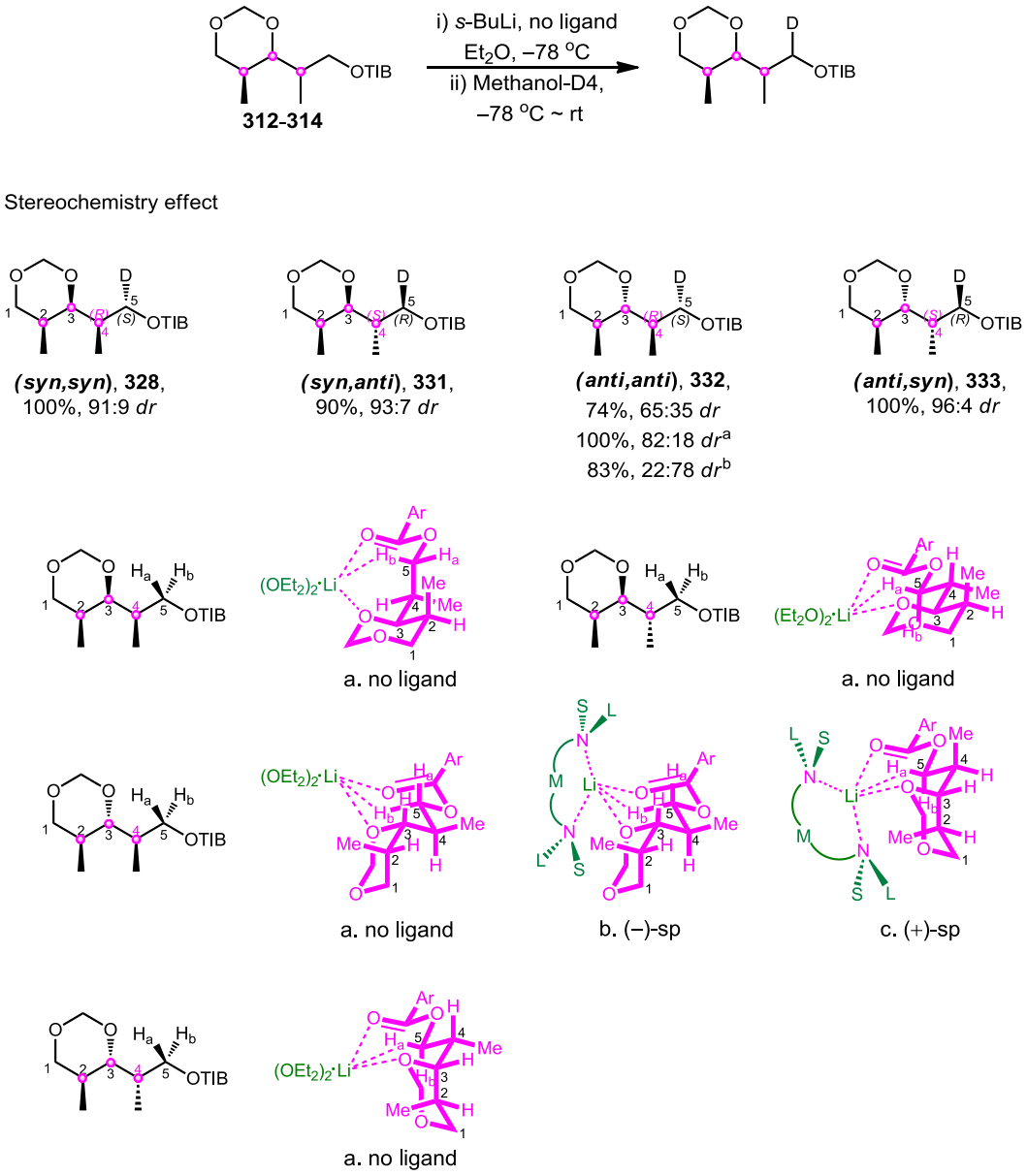

**Scheme 2.31.** Lithiation–Deuteration study on benzoate ester **312**. The yield and *d.r.* were determined by $^1$H NMR.

Afterwards, different protecting groups were screened in the absence of diamine ligand, the results of which are summarised in Scheme 2.32. Compared with silyl groups, acetal groups turned out to be better protecting groups. Benzoate esters protected with acetals produced the products in good yields and high stereoselectivity (**328**, **301a**, **303**, Scheme 2.32), while the silyl protecting groups resulted in lower yields and diastereoselectivity (**328**-**330**, Scheme 2.32). We believe that the coordination of the lithium cation with two oxygen atoms (7-O and 8-O) led to a preference of lithiation of proton $H_b$ affording the observed major isomer (Scheme 2.32).




**Scheme 2.32.** Exploration into the protecting group effect on lithiation in the absence of ligand. The yield and *d.r.* were determined by $^{1}$H NMR.

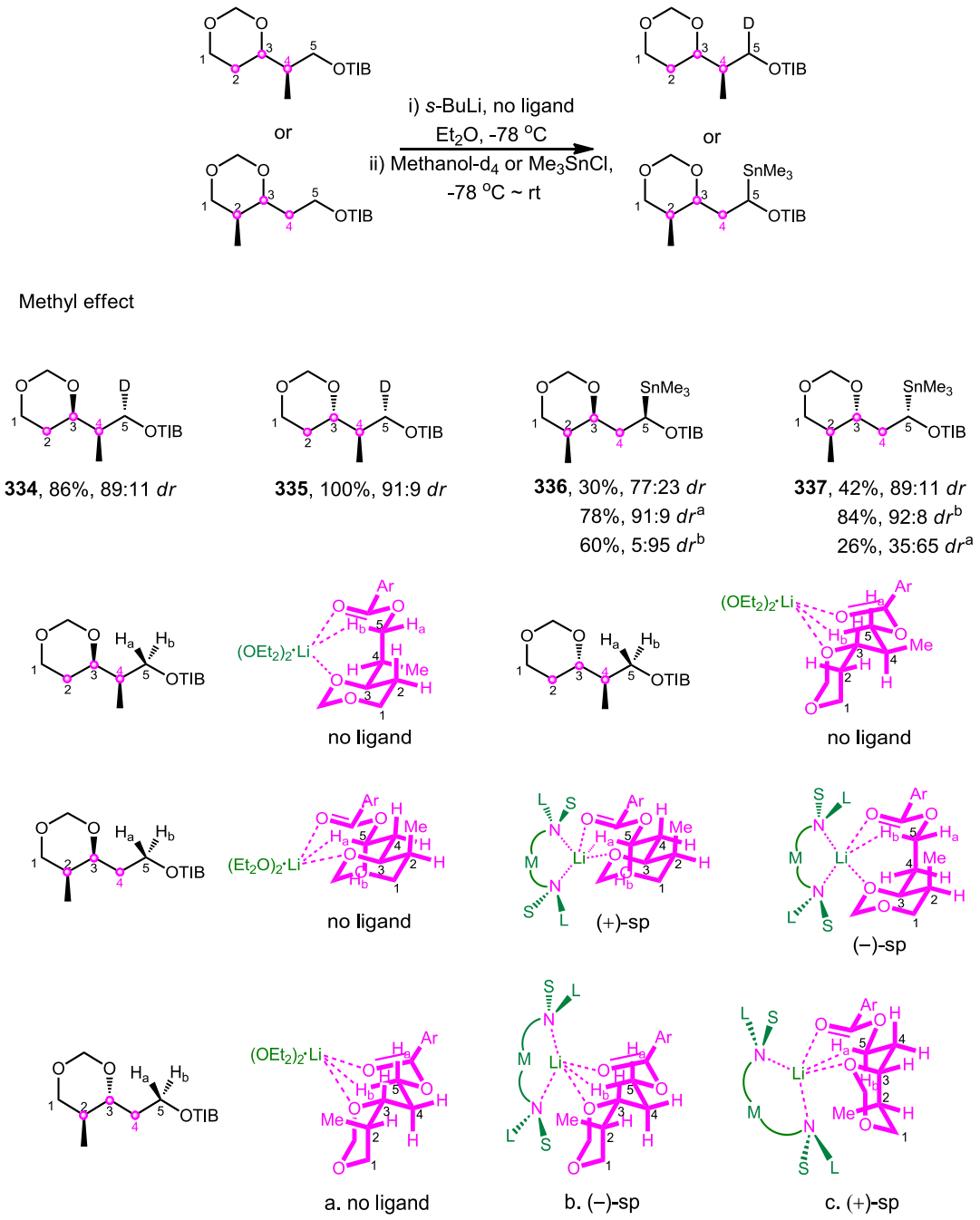
Furthermore, the effect of stereochemistry was explored. To avoid the steric hindrance of protecting groups, benzoate ester **312** and its three stereoisomers were tested. (Scheme 2.33). Poor substrate control was observed with (*anti*, *anti*)-isomer **332**, which was formed in ca. 2:1 *d.r.* (Scheme 2.33). Interestingly, the stereoselectivity can be improved by addition of (–)-sparteine, and while the other diastereoisomer could also be produced in an around 4:1 *d.r.* using (+)-sparteine (Scheme 2.32). On the other hand, strong substrate control was discovered in all other cases, and excellent diastereoselectivity can be obtained. Noticeably, the stereochemistry of deuterium at the 5-position is opposite to the adjacent 4-methyl group in all cases in the absence of additive ligand. This phenomenon can be explained by the *anti*-relationship between the proton to be lithiated and the adjacent 4-methyl group in the favourable conformations (Scheme 2.33).




**Scheme 2.33.** Exploration into the stereochemistry effect on lithiation. The yield and *d.r.* were determined by $^{1}$H NMR; a. (–)-sparteine (2.0 eq.) was added; b. (+)-sparteine (2.0 eq.) was added.

Completing the exploration of the effect of protecting groups and stereochemistry on the diastereoselectivity of the lithiation, the effect of the methyl group position was further investigated (Scheme 2.34). The roles of methyl groups in the 2- and 4-positions were compared, of which the latter was found to be more important. Without a methyl group in the 2-position, the substrate control effect was still strong, and isomers **334** and **335** were formed in good yields and stereoselectivity (**334**, **335**, Scheme 2.34). Poor

levels of substrate control were observed without a methyl group in the 4-position, and the yields dropped substantially (**336**, **337**, Scheme 2.34). Although high levels of reagent control were achieved, different isomers can be produced in high stereoselectivity by using the sparteine ligands (**336**, **337**, Scheme 2.34). Due to the similarity in chemical shift of 5-$H_a$ and 5-$H_b$ of **326** and **327**, the lithiated isomers were trapped with $Me_3SnCl$ (**336**, **337**, Scheme 2.34) to aid analysis.




**Scheme 2.34.** Exploration into the methyl effect on lithiation. The yield and dr were determined by $^1$H NMR. a. (+)-sparteine (2.0 eq.) was added; b. (–)-sparteine (2.0 eq.) was added.

After extensive exploration, it can be concluded that protecting groups, stereochemistry and methyl groups are all important parametres affecting the level of substrate control. Acetals are good protecting groups for the reaction, which generally result in excellent yields and diastereoselectivity. In terms of stereochemistry, (*anti*, *anti*)-isomer **322** showed poor substrate control but higher reagent control, while the other isomers operate under substrate control. It was also discovered that the 4-methyl group played a more significant role than the 2-methyl group.

### 2.2.5. Determination of Diastereoselectivity of Lithiation–Deuteration Reaction

The major and minor diastereomers formed in the lithiation–deuteration of benzoate ester **312** were determined in the following way. All others were assigned by the same analysis.

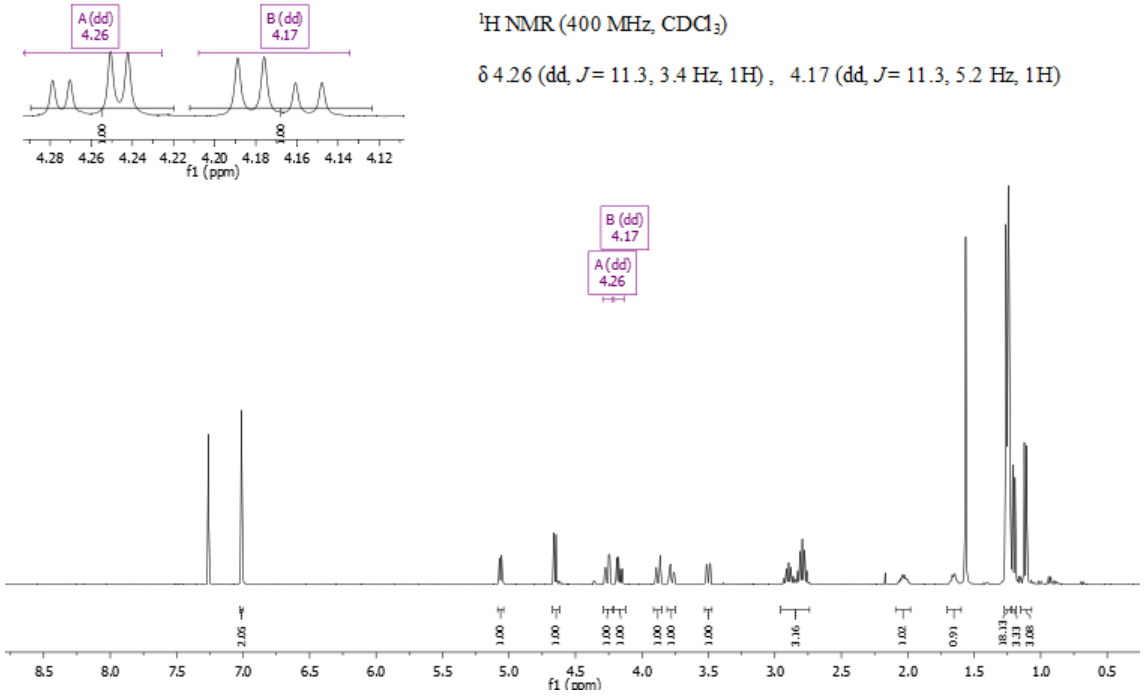



**Figure 2.9.** $^{1}$H NMR spectroscopy of benzoate ester **312**.

The proton signals at $\delta_H$ = 4.26 ppm and $\delta_H$ = 4.17 ppm were assigned as the signal of 5-$CH_2$ of benzoate ester **312** (Figure 2.10) by performing $^{1}$H NMR, $^{13}$C NMR, COSY, HSQC and HMBC experiments.

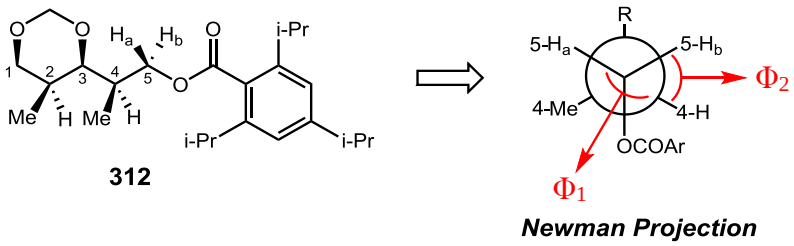
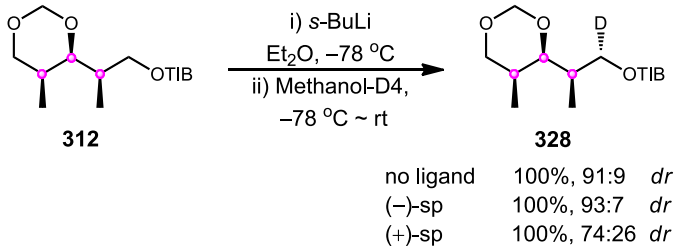



**Figure 2.10.** Benzoate ester **312** and its Newman projection.

According to the Newman projection of benzoate ester **312**, the dihedral angle between 5-C-$H_a$ bond and 4-C-H bond (Φ1) is roughly 180°, while the dihedral angle between 5-C-$H_b$ bond and 4-C-H bond (Φ2) is roughly 60° (Figure 2.10). This is likely to be the most stable conformer and so, according to the Karplus equation, $H_a$ should have a larger vicinal coupling. Consequently, δ 4.17 ($^3J_{5\text{-H-C-C-4-H}}$ = 5.2 Hz) is the signal of 5-$H_a$, and δ 4.26 ($^3J_{5\text{-H-C-C-4-H}}$ = 3.4 Hz) is the signal of 5-$H_b$.

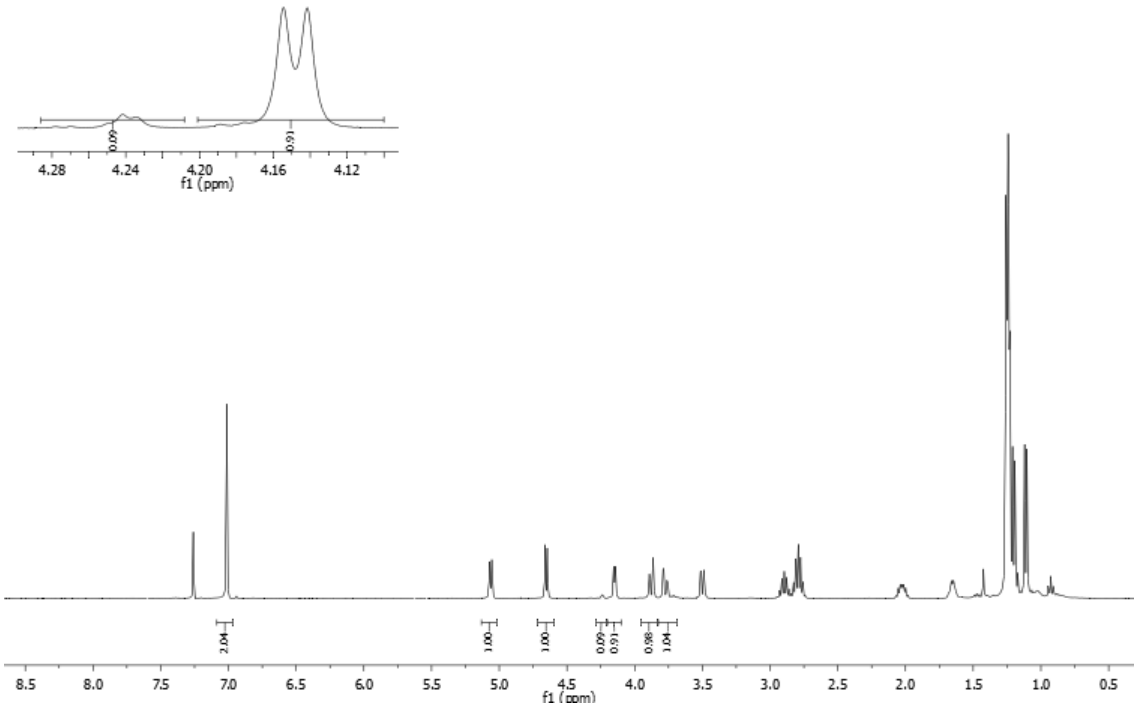



**Scheme 2.35.** Lithiation–deuteration reactions of benzoate ester **312**.

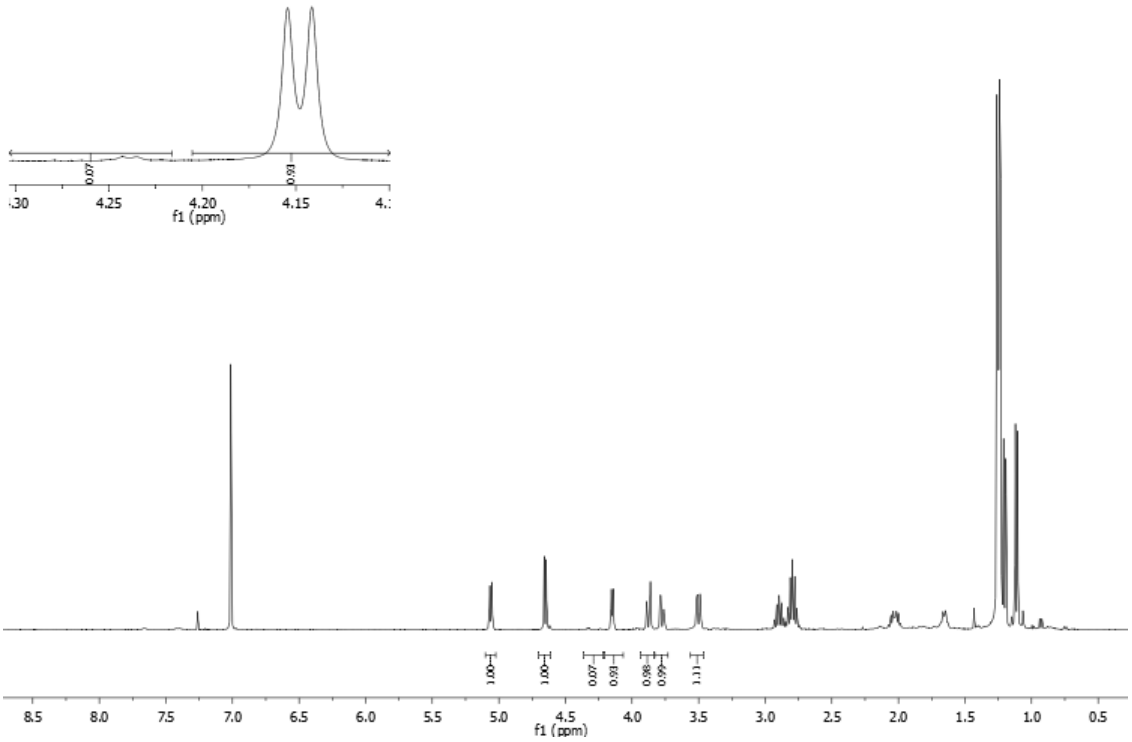
When lithiation–deuteration reaction was conducted in the absence of diamine ligand, 9% of $H_b$ was left, indicating 91% of D-incorporation was obtained; while 91% of $H_a$ was left, indicating 9% of D-incorporation was obtained. Therefore, a complete D-incorporation was obtained with a *dr* of 91:9 (Figure 2.10A). When (–)-sparteine was employed as ligand, 7% of $H_b$ was left, indicating 93% of D-incorporation was obtained; whereas 93% of $H_a$ was left, indicating 7% of D-incorporation was obtained. Consequently, a complete D-incorporation was obtained with a *dr* of 93:7 (Figure 2.10B). In the case of (+)-sparteine, 26% of $H_b$ was left, indicating 74% of D-incorporation was obtained; whilst 74% of $H_a$ was left, indicating 26% of D-incorporation was obtained. As a result, a complete D-incorporation was obtained with a *dr* of 74:26 (Figure 2.10C).

The D-incorporation and *d.r.* of all other lithiation–deuteration reactions in this thesis were determined by the above method.

A). no ligand




B). (–)-sparteine



C). (+)-sparteine

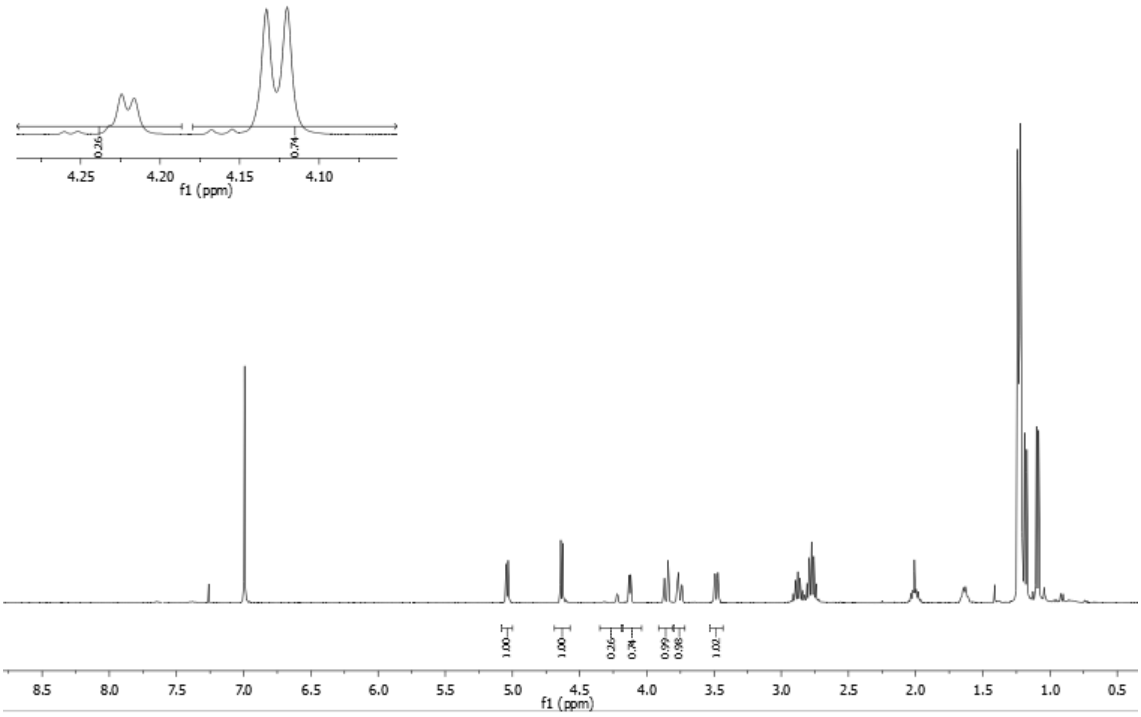



**Figure. 2.10.** $^{1}$H NMR spectroscopy of lithiation-deuteration reactions of benzoate **312**.

### 2.2.6. Assembly of Building Block A3 and D3

To carry on the project, we decided to commence the coupling of building block **A3** and building block **D3** (boronic ester **338**, prepared by Dr. Alba Millan Delgado) (Figure 2.9) via lithiation–borylation reaction. Based on all previous extensive exploration, benzoate esters **306** and **302** were chosen as the substrates to probe the reaction efficiency. Although benzoate **312** can also be well lithiated, it was not used in lithiation–borylation reaction as its protecting group (O-$CH_2$-O) is more difficult to remove.

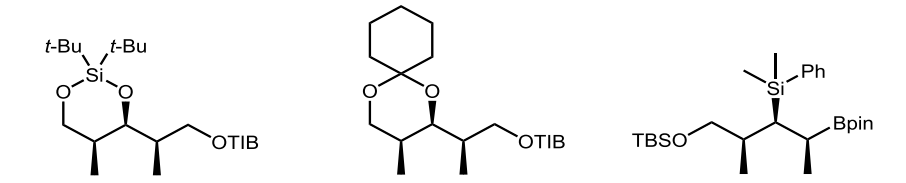
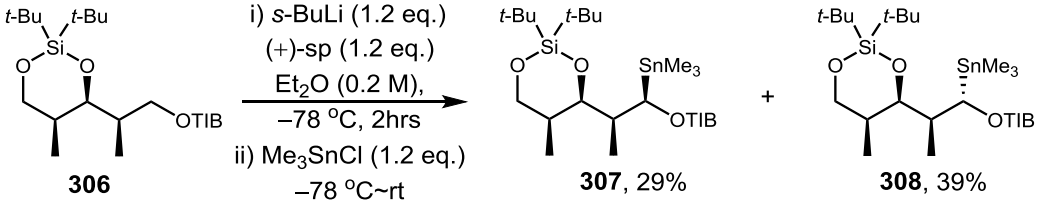



**Figure 2.9.** Building Blocks **A3** and **D3**.

### *2.2.6.1. Lithiation–Borylation of Building Block A3 and Bulky Boronic Ester*

As discussed in **§.**2.2.3.2, we attempted to transform benzoate ester **306** to the corresponding stannanes **307** and **308**, which can provide both desired isomers if they are separable. Firstly, the lithium carbenoid was generated from benzoate ester **306** by treatment with *s*-BuLi and (+)-sparteine in $Et_2O$ at −78 °C. The carbenoid was trapped with addition of $Me_3SnCl$ solution at −78 °C. To our delight, the diastereoisomers **307** and **308** were isolated successfully by flash chromatography on silica gel in yields of 29% and 39% respectively (Scheme 2.35).

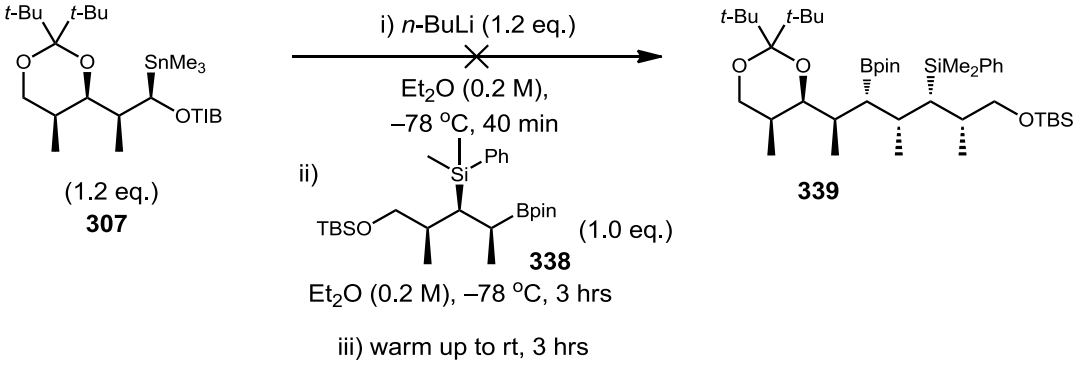



**Scheme 2.35.** Preparation of stannanes using lithiated benzoate ester **306**.

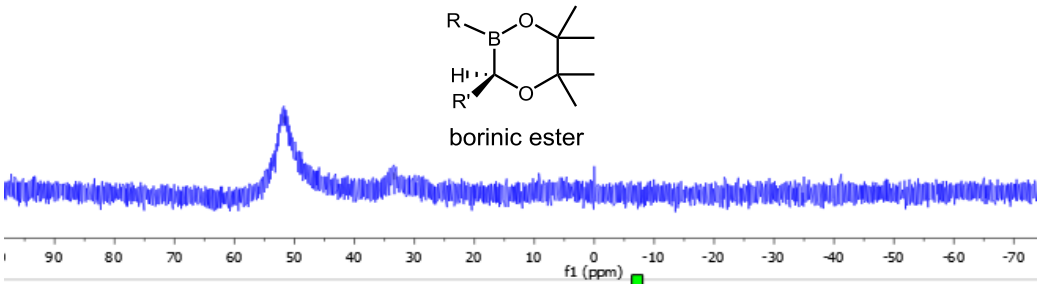
With stannane **307** in hand, we started to investigate the lithiation-borylation reaction with boronic ester **338** (Scheme 2.36). The lithium carbenoid was generated at −78 °C through addition of *n*-BuLi to the requisite stannane and subsequently trapped by addition of chiral boronic ester **338** the reaction was then warmed to room temperature to promote 1,2-metalate rearrangement. The reaction was monitored by $^{11}B$ NMR spectroscopy; however, the signal of desired boronic ester **339** (the chemical shift should be around 33 ppm) was not present, instead a signal at 52 ppm was observed, which indicated the formation of borinic ester (Scheme 2.36B).[166] This phenomenon demonstrated that 1,2-O-migration rather than 1,2-C-migration had occurred, which reasonably resulted from the steric hindrance of boronate complex. The stereospecific 1,2-metalate rearrangement requires an antiperiplanar arrangement of the migrating group on boron and the benzoate ester leaving group. The oxygen atom can be placed antiperiplanar to the leaving group when the steric hindrance prevented the carbon-carbon bond rotation to place the R group in the antiperiplanar. We sought to isolate the unexpected borinic ester. However, we found that the borinic ester was not sufficiently

stable and easily decomposed, and only benzoate ester **306** was recovered which is derived from the reversible decomposition of the boronate complex (Scheme 2.36C).

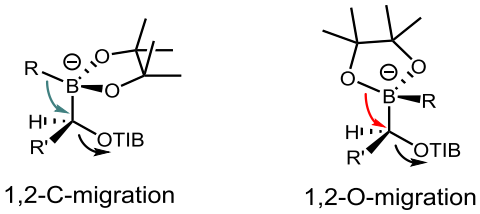
A) Lithiation–borylation reaction of benzoate ester **307**.

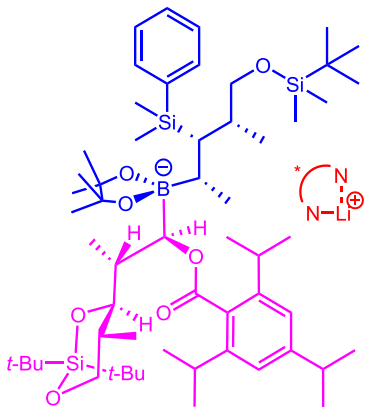



B) $^{11}$B NMR for reaction crude mixture




C) C-migration and O-migration



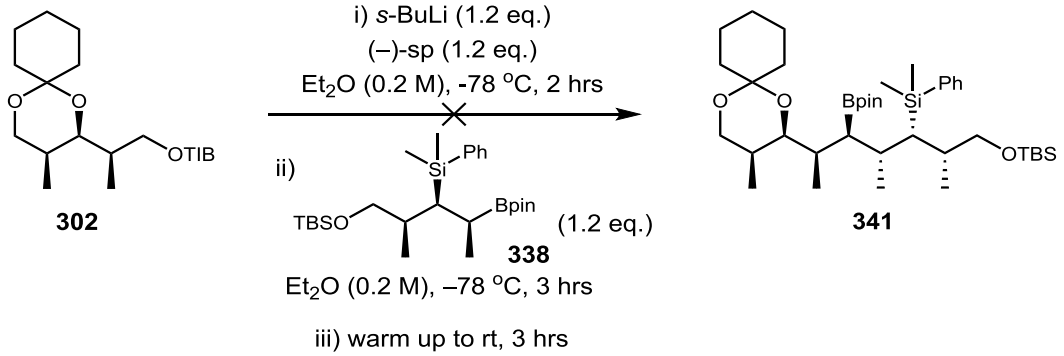




Boronate complex **340**

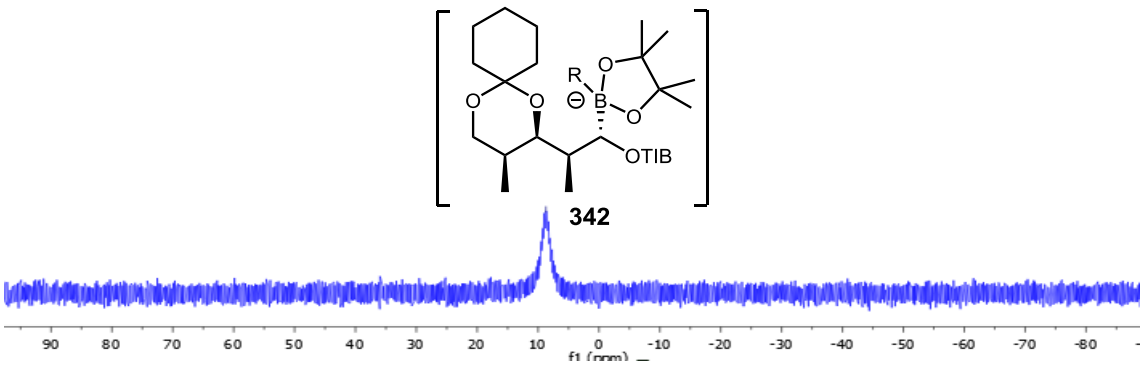
**Scheme 2.36.** Lithiation–borylation reaction study on stannane **307.**

We reasoned that decreasing the steric hindrance of boronate complex can help avoid or reduce 1,2-O-migration. We thus continued to investigate the reaction with benzoate ester **302**, which is less hindered than **307** as it has a smaller protecting group (Scheme 2.37A). This was treated with a chiral base complex (*s*-BuLi/(–)-sparteine) to generate the corresponding chiral organolithium followed by electrophilic substitution by addition of chiral boronic ester **338**. The generated chiral boronate complex was confirmed by $^{11}$B NMR spectroscopy (Scheme 2.37B). However, the desired product **341** was not detected after warming to room temperature, and complete O-migration was observed once again.

A) Lithiation–borylation reaction of benzoate ester **302**

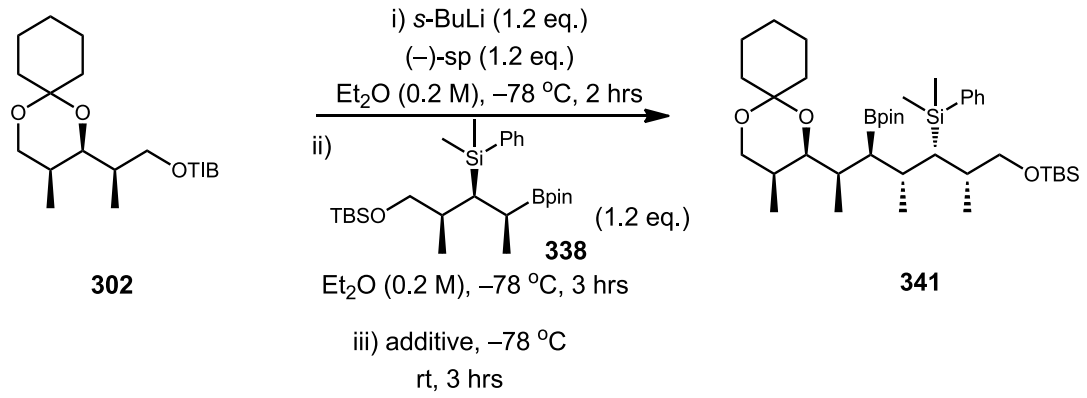



B) $^{11}$B NMR for 'ate' complex formation




**Scheme 2.37.** Lithiation–borylation reaction study on benzoate ester **302**.

**Table 2.10.** Attempted optimisation of lithiation–borylation reaction of benzoate ester **302.**[a]

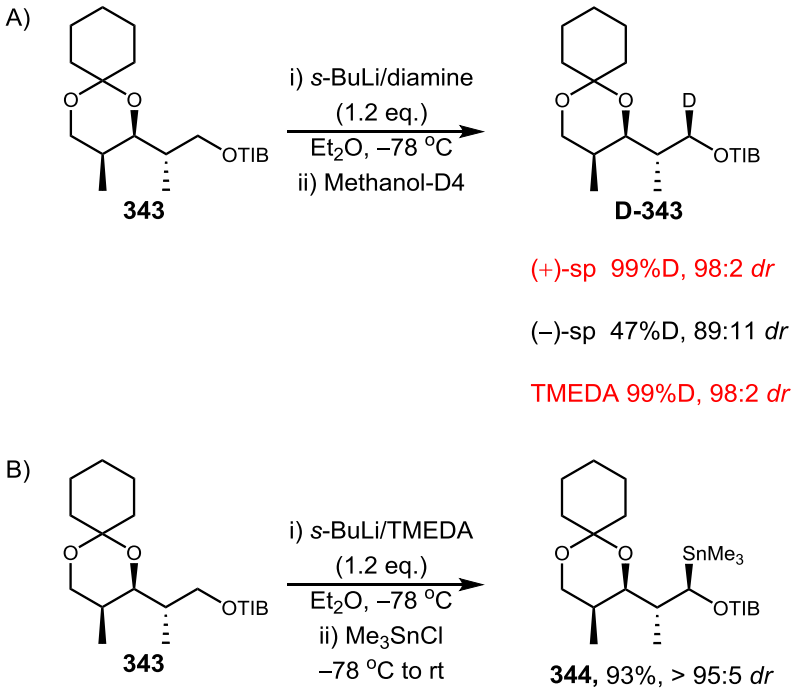



| Entry | Solvent | Additive | Results[b] |
|---|---|---|---|
| 1 | $Et_2O$ | -- | O-migration, No porduct |
| 2 | TBME | -- | O-migration, No porduct |
| 3 | CPME | -- | O-migration, No porduct |
| 4 | $Et_2O$ to $CHCl_3$ | -- | O-migration, No porduct |
| 5 | $Et_2O$ | Addition of BE in THF | O-migration, No porduct |
| 6 | $Et_2O$ | $MgBr_2{\cdot}OEt_2$ | O-migration, No porduct |
| 7 | $Et_2O$ | $OH(CH_2)_2OH$ | O-migration, No porduct |

[a.] Benzoate ester **302** (50 mg) was employed in the reaction, and boronic eater **338** was added in $Et_2O$; [b.] O-migration was detected by $^{11}B$ NMR spectroscopy.

To address this problem, we decided to optimise the reaction conditions. However, the initial effort did not lead to any positive results. Alternative solvents were tested, but the same results as when using $Et_2O$ were obtained (Entry 1-2, Table 2.10). Solvent exchange to non-coordinated $CHCl_3$ after boronate complex formation did not promote the 1,2-C-migration (Entry 3, Table 2.10). The addition of a THF solution of boronic ester did not improve the reaction (Entry 4, Table 2.10). Additives that were considered to promote the C-migration (Entry 6, Table 2.10) or inhibit the boronate complex reversibility (Entry 7, Table 2.10) also failed in promoting this reaction. No desired product was formed in all cases.

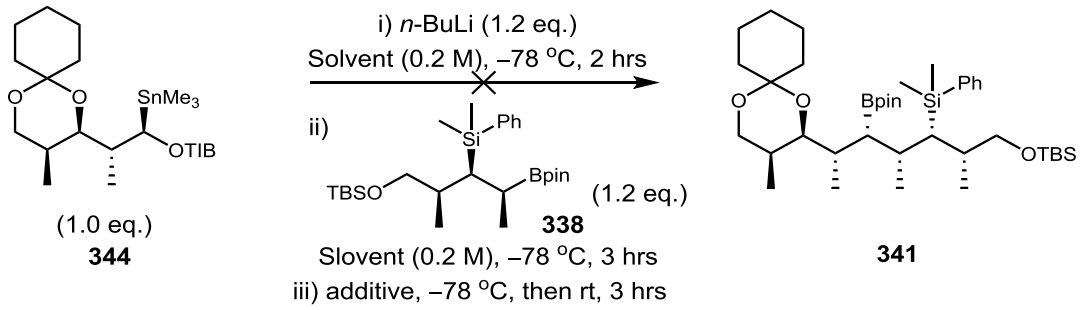
An alternative to reduce the congestion of boronate complex is to carry out the reaction under diamine free conditions. Therefore, we sought to synthesise the corresponding stannane. Since we found that benzoate ester **343** can be lithiated in excellent diastereoselectivity in the presence of less valuable (+)-sparteine or TMEDA, we chose benzoate ester **343** to prepare the corresponding stannane **344** (Scheme 2.38).




**Scheme 2.38.** Preparation of stannane **344**.

With stannane **344** in hand, we continued to test the lithiation–borylation reaction with boronic ester **338**. The reaction was performed in a variety of common ethers and coordinating solvent THF, but no desired product was obtained in all these cases (Entry 1-4, Table 2.11), instead O-migration was observed exclusively. The solvent exchange and addition of Lewis acid or a diol were also ineffective (Entry 5-8, Table 2.11). All these attempts failed to promote the desired C-migration over O-migration, and no desired product was formed.

**Table 2.11.** Attempted optimisation of lithiation–borylation reaction with stannane **344**.[a]

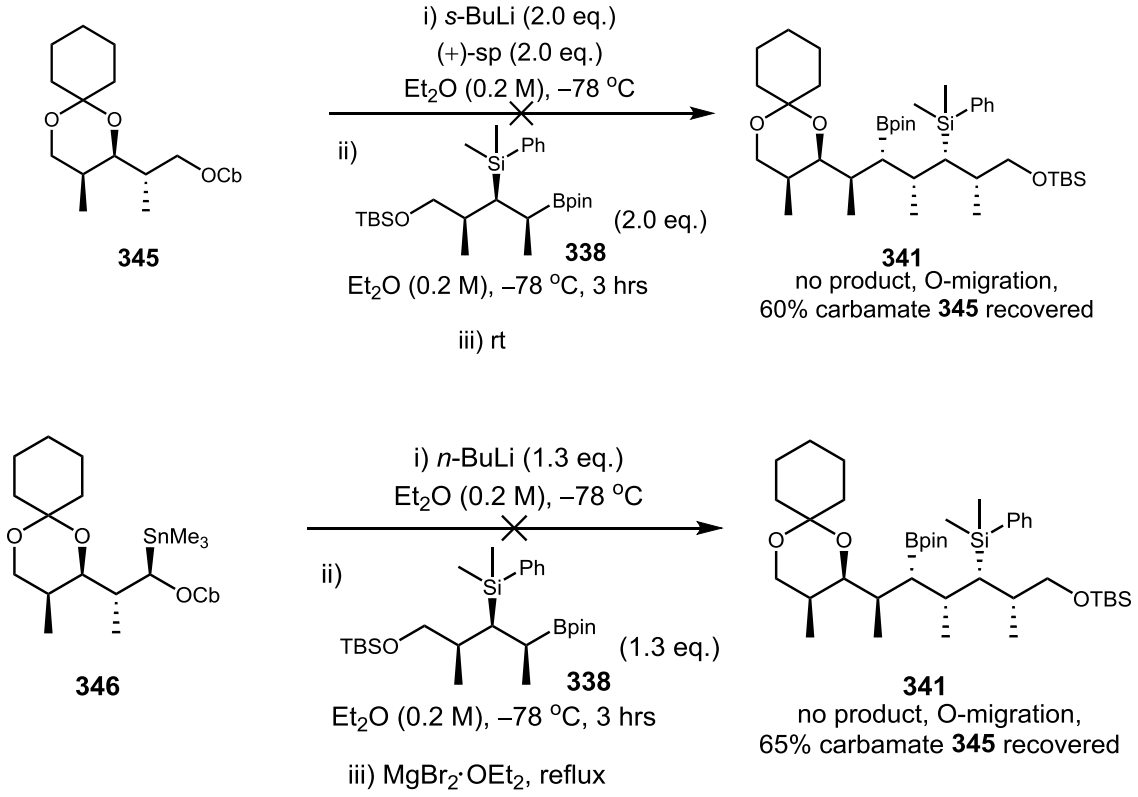



| Entry | Solvent | Additive | Results[b] |
|---|---|---|---|
| 1 | $Et_2O$ | -- | O-migration, 30% benzoate |
| 2 | TBME | -- | O-migration, 18% benzoate |
| 3 | CPME | -- | O-migration, 16% benzoate |
| 4 | THF | -- | O-migration, complex |
| 4 | $Et_2O$ to $CHCl_3$ | -- | O-migration, complex |
| 5 | $Et_2O$ | Addition of BE in THF | O-migration, complex |
| 6 | $Et_2O$ | $MgBr_2{\cdot}OEt_2$ | O-migration, 17% benzoate |
| 7 | $Et_2O$ | $MgBr_2{\cdot}MeOH$ | O-migration, complex |
| 8 | $Et_2O$ | $OH(CH_2)_2$ OH | O-migration, 23% benzoate |

[a.] Stannane **344** (50 mg) was employed in the reaction, and boronic eater **338** was added in $Et_2O$; [b.] O-migration was detected by $^{11}B$ NMR spectroscopy.

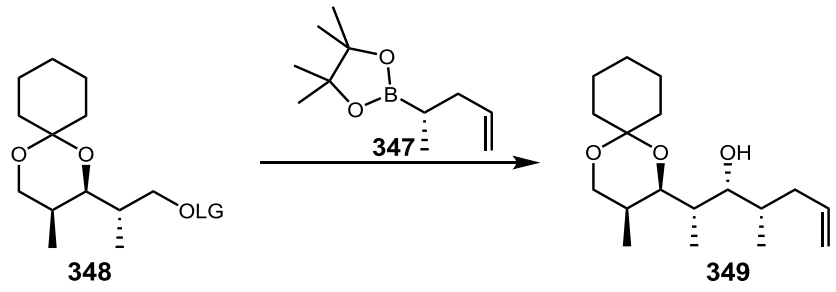
We previously found within our group that the balance between O-migration and C-migration can be influenced by the nature of leaving group[167] and so we explored the use of carbamate **345** and the corresponding stannane **346** (Scheme 2.39) in place of benzoate ester **302**. The reaction was carried out under reported conditions. Carbamate **345** was lithiated with *s*-BuLi in the presence (+)-sparteine and trapped by the addition of boronic ester **338** at –78 °C. After that the reaction was warmed to room temperature to promote 1,2-migration. While stannane **346** was reacted with boronic ester **338** under diamine free conditions using *n*-BuLi as base and Lewis acid $MgBr_2{\cdot}Et_2O$ was

added to promote 1,2-migration at reflux conditions. Unfortunately, the strategy did not work in this reaction, and O-migration occurred once again (Scheme 2.39).




**Scheme 2.39.** Lithiation–borylation using cyclic carbamate.

### *2.2.6.2. Lithiation–Borylation of Building Block A3 and Less Hindered Boronic Ester*

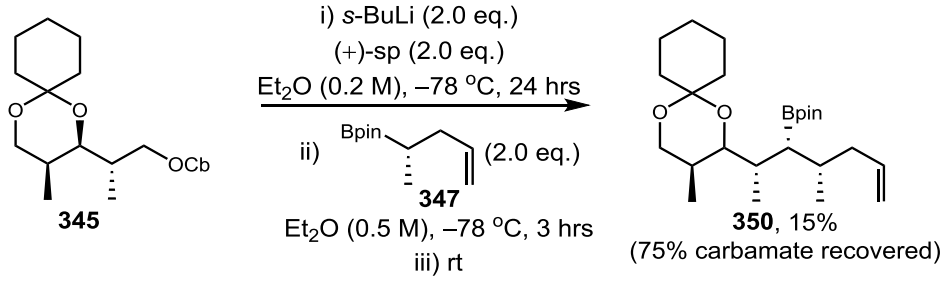



**Scheme 2.40.** Lithiation–borylation using less hindered boronic ester **347**.

Based on the above exploration, we believed that the congestion of building block **D3** (boronic ester **338**) was the key factor preventing the coupling reaction. We thus decided to seek a less hindered boronic ester, and consequently boronic ester **347**

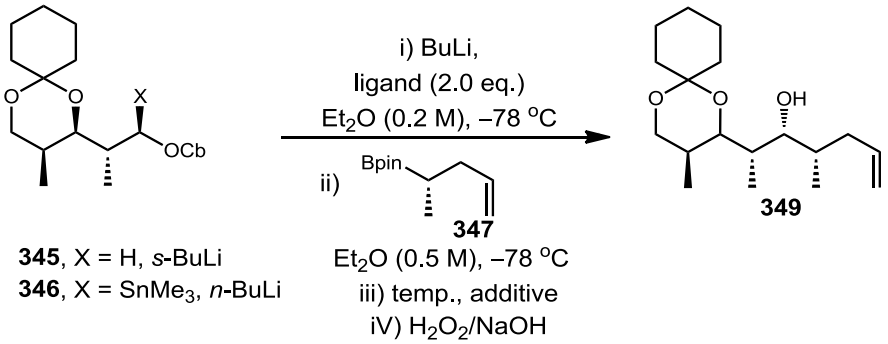
(provided by Dr. Daniel Pflasterer) was chosen as the new building block to continue the exploration (Scheme 2.40).

The exploration commenced with the lithiation–borylation of carbamate **345**, which was deprotonated by treatment with *s*-BuLi/(+)-sparteine and followed by subsequent borylation and migration. Pleasingly, desired boronic ester **350** was obtained, albeit in low yield (15%, Scheme 2.41). The recovery of carbamate **345** (75%, Scheme 2.40) indicated the reversibility of the boronate complex formation step, whilst no O-migration was observed. The reaction was subjected to further optimisation. The temperature was increased to promote the 1,2-metelate rearrangement, and product was yielded in marginally higher yield (Entry 2, Table 2.12). However, O-migration was observed at elevated temperature indicating both C-migration and O-migration were accelerated. We compared the reactivity of carbamate **345** and stannane **346** (Entry 3-4, Table 2.12). The stannane first reacted with boronic ester **347** to form the desired boronate complex, before addition of Lewis acid $MgBr_2$·MeOH heating the reaction mixture to reflux to allow the migration step to proceed. The yield was significantly increased; however, more O-migration also occurred (Entry 3, Table 2.12). Addition of $MgBr_2$·MeOH with migration at room temperature led to less O-migration, but a decrease in yield was also detected (Entry 4, Table 2.12). Based on the exploration, carbamate **345** or its corresponding stannane **346** was not the best choice for this lithiation–borylation reaction.




**Scheme 2.41.** Lithiation–borylation of carbamate **345** and boronic ester **347**.

**Table 2.12:** Optimisation of Lithiation–borylation reaction with carbamate and carbamate stannane.




| Entry | Compound | Temp (°C) | Ligand | Additive | Yield[a](%) | $C_{mig}$ : $O_{mig}$[b] |
|---|---|---|---|---|---|---|
| 1 | **345** | rt | (+)-sp | -- | 15(75) | 100:0 |
| 2 | **345** | 45 | (+)-sp | -- | 36(46) | 65:35 |
| 3 | **346** | 45 | -- | $MgBr_2$·MeOH | 53(21) | 60:40 |
| 4 | **346** | rt | -- | $MgBr_2$·MeOH | 27(35) | 70:30 |

[a.] Isolated yield of compound **349**, the yield in parenthesis was the yield of recovered carbamate; [b.] the ratio was determined by $^{11}B$ NMR spectroscopy.

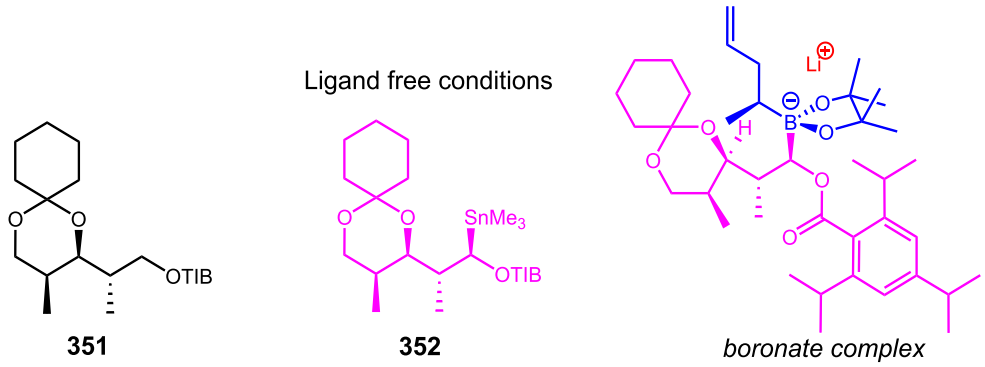
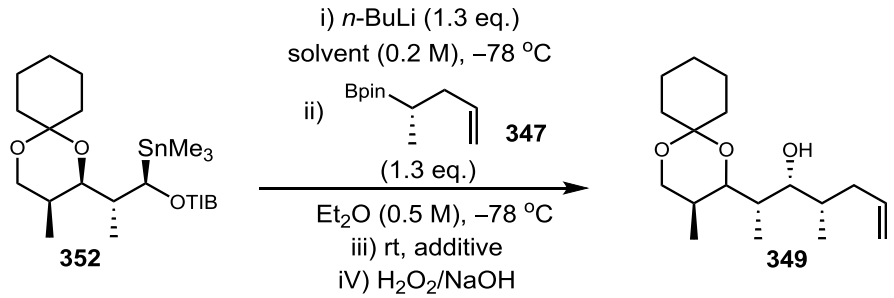



**Figure 2.10.** Possible ways to reduce steric hindrance of boronate complex.

As the carbamate did not provide satisfactory results, we continued to optimise the reaction with benzoate ester **351** (Figure 2.10). As diamine free conditions can provide a comparatively less congested boronate complex, benzoate stannane **352** was tested first (Table 2.13).

**Table 2.13:** Optimisation of Lithiation–borylation reaction with benzoate ester stannane **352**.

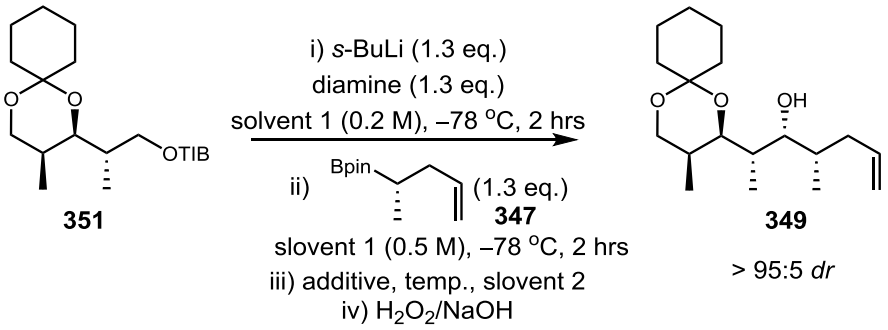



| Entry | Temp (°C) | Additive | Yield[a](%)[a] | $C_{mig}$ : $O_{mig}$[b] |
|---|---|---|---|---|
| 1 | rt | -- | 42(29) | 50:50 |
| 2 | rt | $MgBr_2 \cdot Et_2O$ | 35(30) | 63:37 |
| 3 | rt | $MgBr_2 \cdot MeOH$ | -- | -- |

[a.] Isolated yield of compound **349**, the yield in parenthesis was the yield of recovered benzoate ester; [b.] the ratio was determined by $^{11}B$ NMR spectroscopy.

Stannane **352** firstly underwent the lithiation–borylation using *n*-BuLi as base without any additive Lewis acid (Entry 1, Table 2.13). The reaction produced the desired product **349** in 42% yield, which was lower than the previous best results provided by carbamate stannane **345** (53%, Entry 3, Table 2.12), whilst 29% of benzoate ester **351** was obtained and O-migration was also observed (C-migration : O-migration = 50:50). The addition of Lewis acid did not result in any improvement. The use of $MgBr_2 \cdot Et_2O$ led to a decrease in O-migration but afforded the product in lower yield (Entry 2, Table 2.13), while $MgBr_2 \cdot MeOH$ resulted in a complex reaction without any product produced (Entry 3, Table 2.13). As no better result was obtained, we stopped the optimisation with stannane **352**.

**Table 2.14:** Optimization of Lithiation–borylation reactions with benzoate ester **351**.




| Entry | Solvent 1 | Solvent 2 | Temp. (°C) | Ligand | Additive | Yield[a] (%) | $C_{mig}$ : $O_{mig}$[b] |
|---|---|---|---|---|---|---|---|
| 1 | $Et_2O$ | $Et_2O$ | rt | (+)-sp | -- | 60(23) | 75:25 |
| 2 | $Et_2O$ | $Et_2O$ | rt | TMEDA | -- | 52(19) | 75:25 |
| 3 | $Et_2O$ | $Et_2O$ | 45 | (+)-sp | -- | 22(62) | 67:33 |
| 4 | $Et_2O$ | $Et_2O$ | rt | (+)-sp | $MgBr_2{\cdot}OEt_2$ | 38(29) | 75:25 |
| 5 | $Et_2O$ | $Et_2O$ | rt | (+)-sp | $MgBr_2{\cdot}MeOH$ | -- | 0:100 |
| 6 | $Et_2O$ | $Et_2O$ | 45 | (+)-sp | $MgBr_2{\cdot}MeOH$ | -- | 0:100 |
| 7 | $Et_2O$ | $Et_2O$ | rt | (+)-sp | $Mg(ClO_4)_2{\cdot}$TFE (2 eq.) | -- | 0:100 |
| 8 | $Et_2O$ | $Et_2O$ | rt | (+)-sp | $Mg(ClO_4)_2{\cdot}$TFE (4 eq.) | -- | 0:100 |
| 9 | $Et_2O$/ THF[c] | THF | rt | (+)-sp | -- | 45 (37) | 100:0 |
| 10 | $Et_2O$ | $CHCl_3$ | 65 | (+)-sp | -- | not detected | 0:100 |

[a.] Isolated yield of compound **349**, the yield in parenthesis is that of recovered benzoate ester **351**; [b.] the ratio was determined by $^1$H NMR; [c.] the benzoate was lithiated in $Et_2O$, and boronic ester **347** was added in THF.

Next, we carried on investigating lithiation–borylation reactions with benzoate ester **351**. The use of (+)-sparteine or TMEDA afforded the desired product in moderate yield and with excellent diastereoselectivity (Entry 1-2, Table 2.14). It was noticed that the O-migration was still observed but occurred to a lesser extent (Entry 1-2, Table 2.14). As higher yield was obtained when using (+)-sparteine, we continued to optimise the reaction in the presence of (+)-sparteine. We further screened the reaction conditions for the migration step by refluxing, addition of Lewis acid and solvent exchange (Entry 3-10, Table 2.14). The elevated temperature led to more serious reversibility with more benzoate ester recovered (Entry 3, Table 2.14). The addition of $MgBr_2{\cdot}OEt_2$ resulted in a lower yield (Entry 4, Table 2.14). The use of $MgBr_2{\cdot}MeOH$ led to complete O-

migration, whilst the stronger Lewis acid $Mg(ClO_4)_2$·TFE also gave comparable results, which demonstrated that these Lewis acids promoted O-migration over C-migration (Entry 5-8, Table 2.14). The solvent was also screened, but unfortunately a solvent exchange to THF or $CHCl_3$ gave no improvement to the reaction (Entry 9-10, Table 2.14). With addition of boronic ester **347** in THF instead of $Et_2O$, only 45% of product formed together with reversibility (Entry 9, Table 2.14); no O-migration was observed under these conditions, which was possibly due to the instability of O-migration product in THF. When the solvent for migration was varied from $Et_2O$ to chloroform, the reaction became very messy, and complete O-migration occurred.

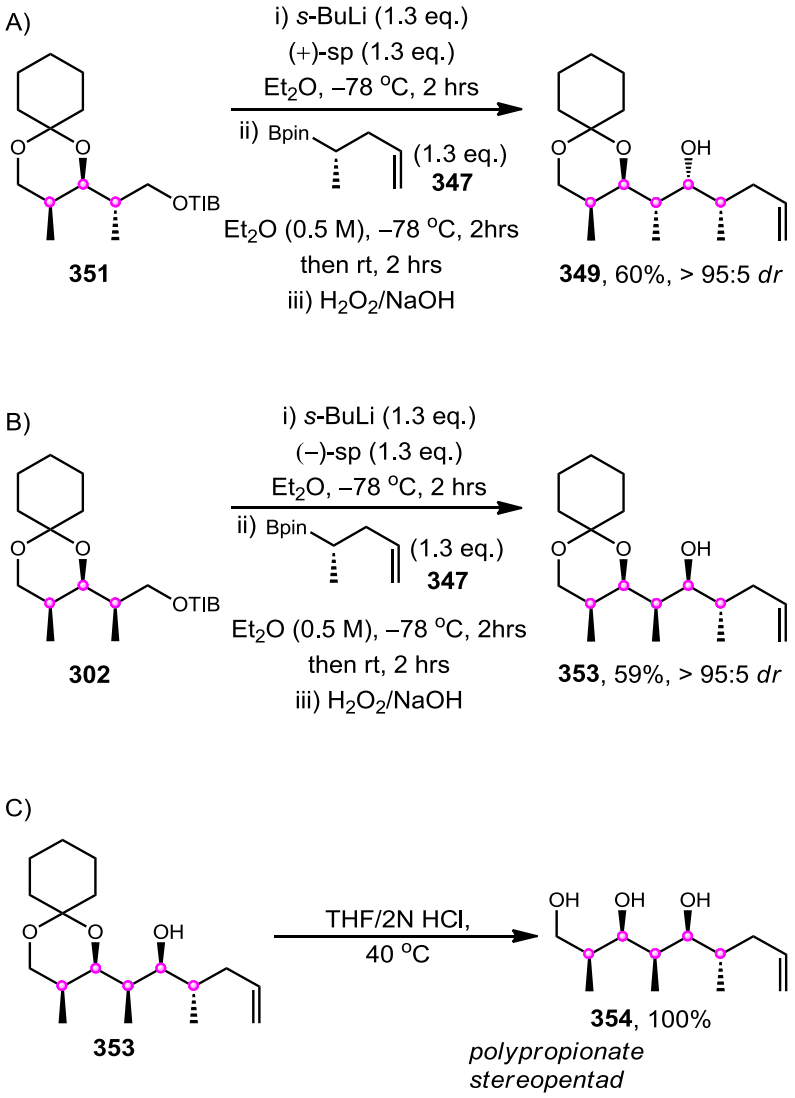
Based on the above phenomena, it can be concluded that all attempts accelerated the O-migration or reversibility of the boronate complex over the desired C-migration. As a result, the best yield can be achieved when the migration was performed at room temperature without any additives (60%, Entry 1, Table 2.14).

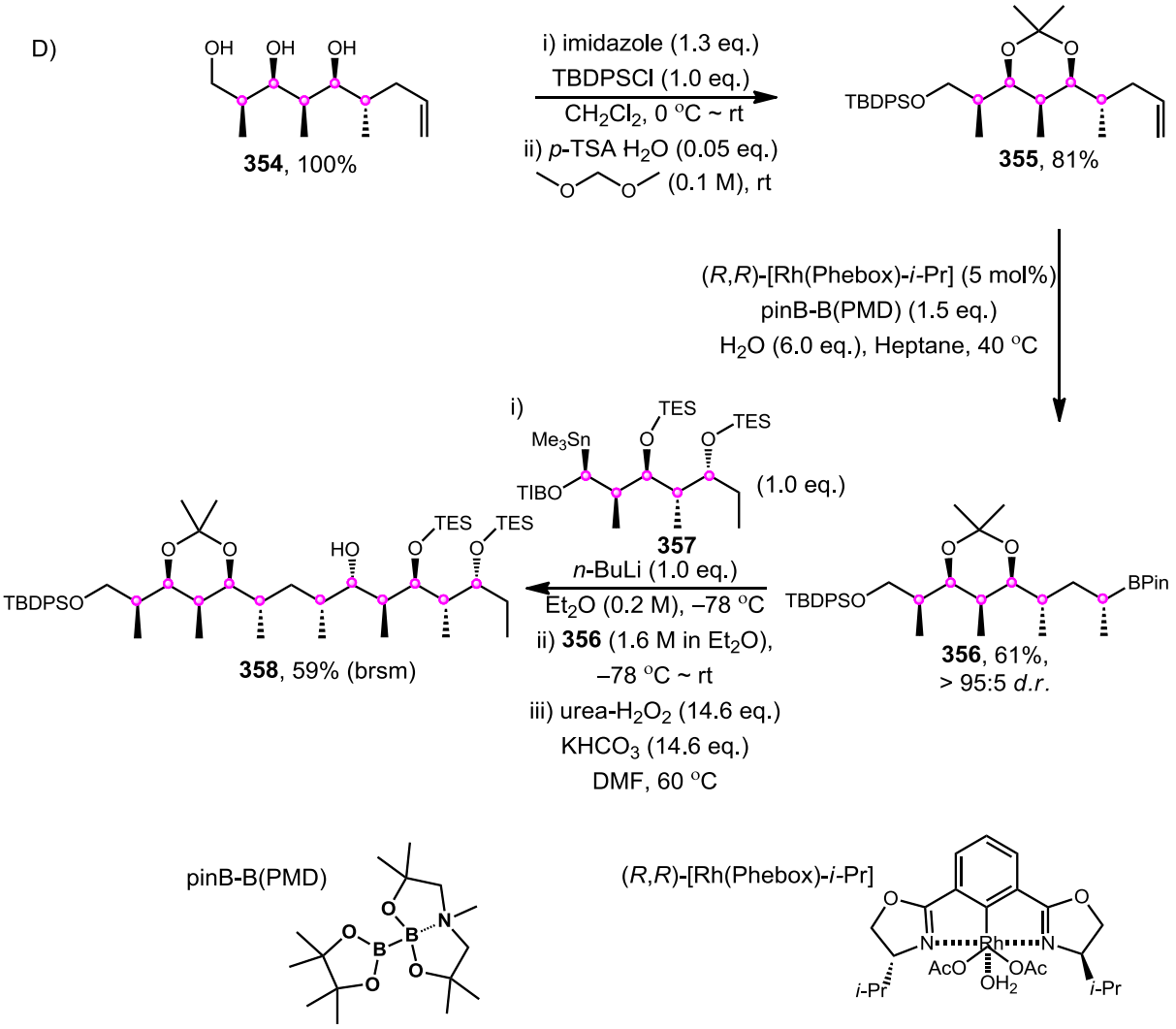
### 2.2.7. Synthetic Application in Polypropionate Fragment Synthesis

After obtaining optimal conditions for the building block coupling, the method was applied to the synthesis of polypropionate motifs. Lithiation–borylation of building block **A3** and boronic ester **347** afforded the desired product in good yields and with excellent stereoselectivity. Different isomers can be prepared using the same procedure (Scheme 2.42A, B). The polypropionate stereopentad **354** can be obtained quantitatively by subsequent deprotection under acidic conditions (Scheme 2.42C), which was further applied in the synthesis of polypropionate fragment **358** (Scheme 2.42D) via subsequent protection, hydroboration and lithiation–borylation–oxidation with **357** (provided by Dr. Daniel Pflasterer).

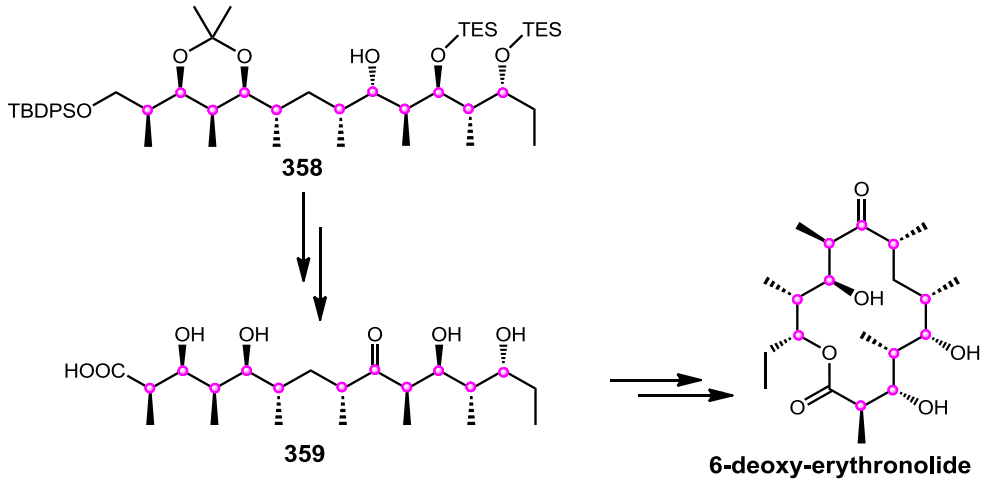
Triol **354** was converted to compound **355** in good yield via protection with TBDPSCl and acetal group. Compound **355** further underwent rhodium-catalysed hydroboration reaction, affording boronic ester **356** in moderate yield and excellent stereoselectivity. Compound **356** was subsequently subjected to the reaction with compound **357**, via lithiation–borylation–oxidation reaction, furnishing fragment **358** in moderate yield (Scheme 2.42D). This fragment is a key intermediate in the synthesis of 6-deoxy-

erithronolide, the total synthesis of which is currently under investigation within our group (Scheme 2.43).






**Scheme 2.42.** Synthetic Applications in polypropionate fragment synthesis.

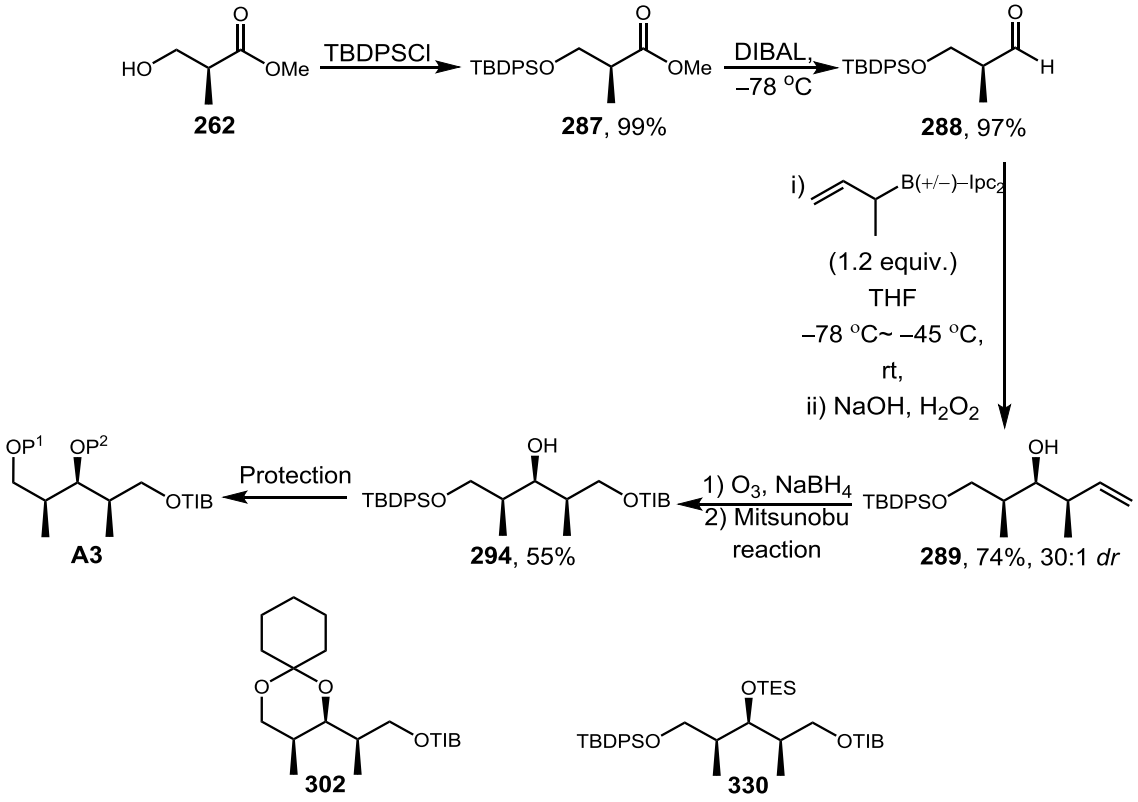



**Scheme 2.43.** 6-deoxy-erythronolide.

## *2.3. Conclusions*

An efficient method for the synthesis of polypropionate fragment based on building block assembly strategy using lithiation–borylation reaction has been developed. Some limitations, such as strong substrate control and O-migration, also existed.

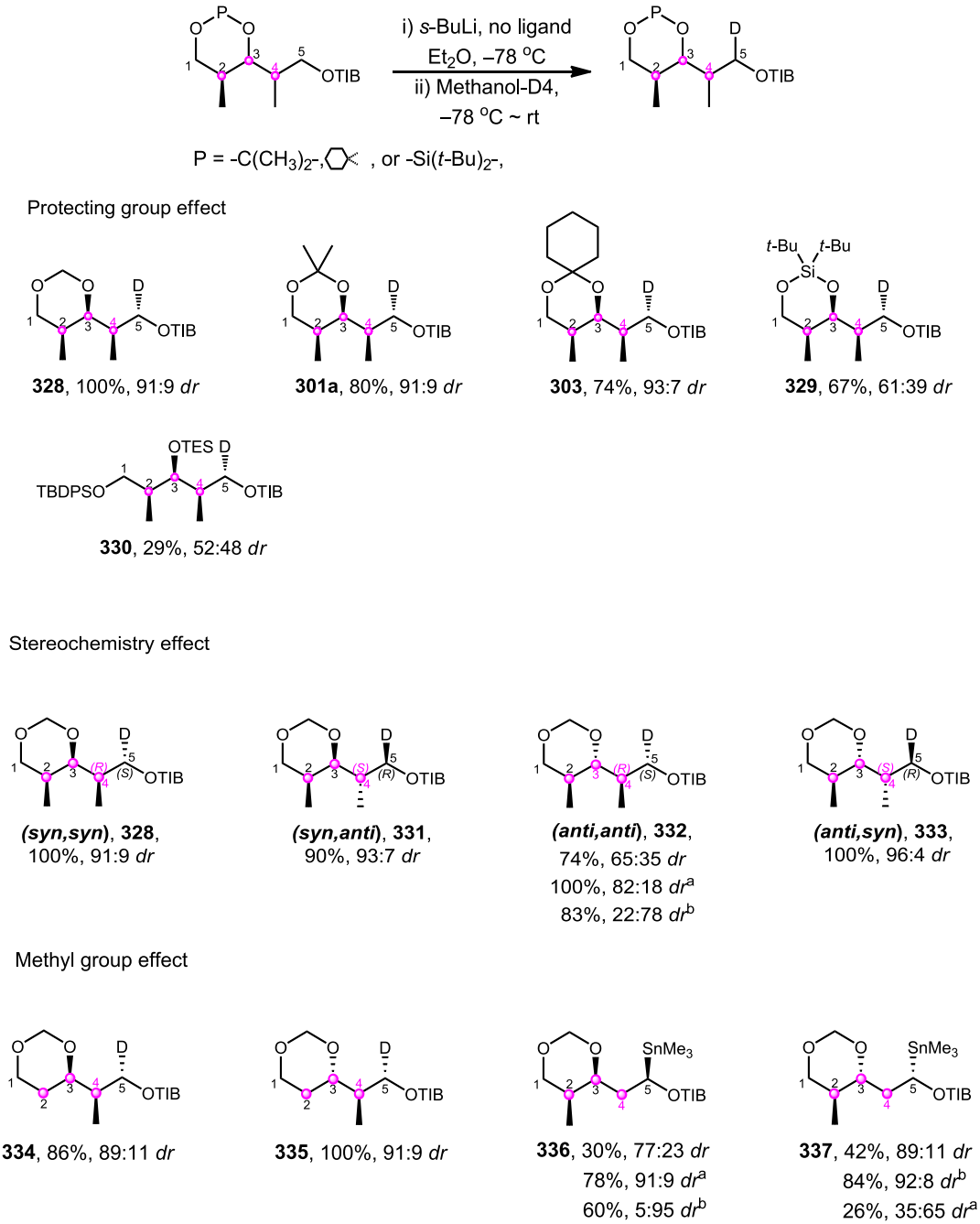
Firstly, we successfully synthesised a series of building blocks, bearing silyl(acyclic) and acetal(cyclic) protected carbamates and benzoate esters (Scheme 2.44) and intensively investigated. The stereoselectivity of building blocks were tested by lithiation–deuteration reactions, and acetal-containing building blocks were efficient in lithiation reactions, giving the products with excellent diastereoselectivity.




**Scheme 2.44.** Preparation of building blocks **A3**.

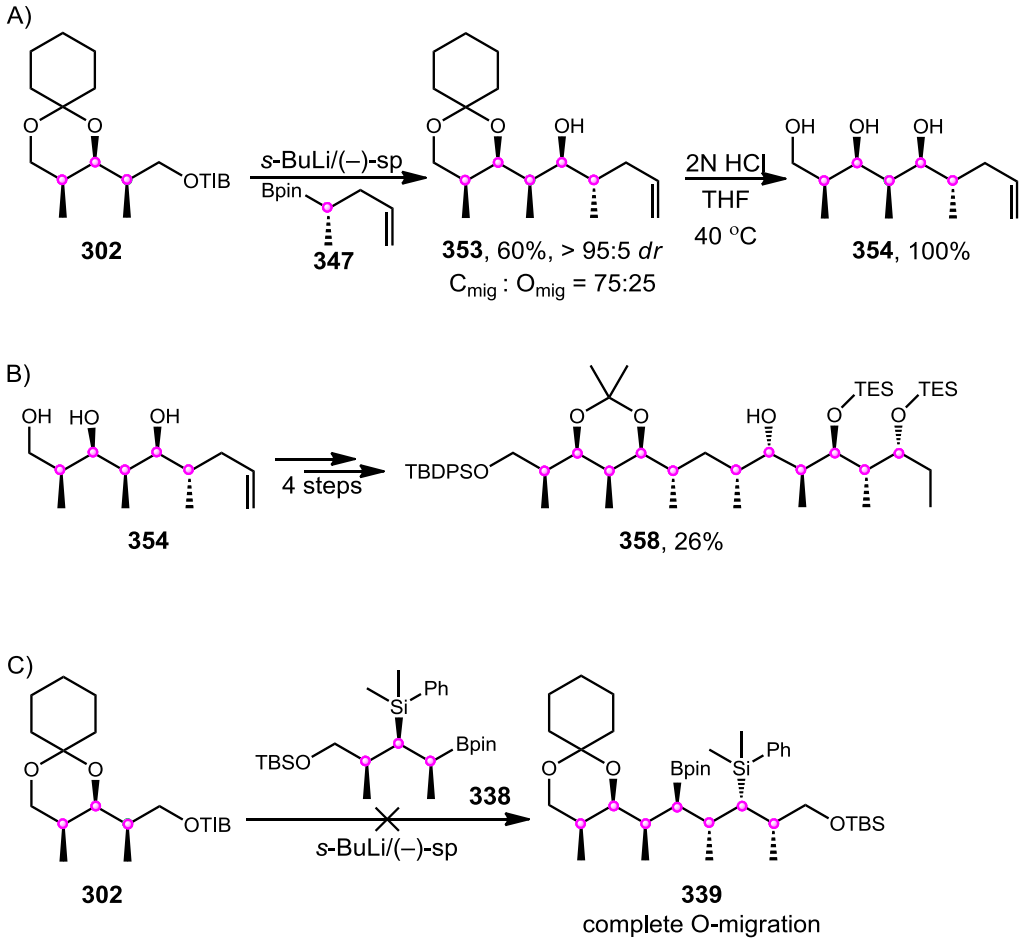
Secondly, we studied the substrate control effect of cyclic building blocks (Scheme 2.45). It was discovered that protecting groups, stereochemistry and methyl groups in the 2- and 4-position are all important factors affecting the substrate control effect. Acetals are good protecting groups for the reaction, which normally leads to excellent

yields and diastereoselectivity. In terms of stereochemistry, (*anti*, *anti*)-isomer demonstrated poor substrate but higher reagent control, while the other isomers displayed strong substrate control. It was also discovered that 4-methyl group had a more significant effect than the 2-methyl group.




**Scheme 2.45.** Substrate control effect of building blocks **A3**.

Thirdly, the reaction conditions for building blocks assembly via lithiation-borylation methodology were extensively investigated. Stereopentad **354** was obtained in good yield and excellent diastereoselectivity when benzoate ester **302** was reacted with boronic ester **347** (Scheme 2.45A). Stereopentad **354** can be further applied in the synthesis of polypropionate fragment **358** (Scheme 2.46B). But there are also limitations that benzoate ester cannot react with bulky boronic ester **338** efficiently, which usually leads to serious O-migration, owing to strong steric hindrance within the boronate complex (Scheme 2.46C).




**Scheme 2.46.** Assembly of building block **A3** and **D3**.

# 3. Exploration of Polyfluoromethylation Reactions of Organoboronic Esters

## *3.1. Introduction and Project Aims*

Fluorine is a small atom with a big ego, the introduction of which into organic compounds often results in unusual properties and behaviour; the fluorinated functional groups confer higher metabolic stability, and lipophilicity, based on their unique chemical, biological and physical properties.[168]

Particularly, the difluoromethyl ($CF_2H$) group is of great importance, and can serve as bio-isosteres of carbinol, thiol, hydroxamic acid, or amide group.[169,170] Thus, the $CF_2H$ group is routinely introduced into the lead medicine molecules in place of the hydroxyl, amino, and thio substituents.[171,172] The $CF_2H$ group is weakly acidic[169] and can serve as hydrogen-bonding donors to increase the bonding selectivity of the bioactive compounds.[170] Consequently, the $CF_2H$ group widely exists in the area of pharmaceuticals and agrochemicals design (Figure 3.1). For instance, Roflumilast **359**[173] can be used to cure obstructive pulmonary disease; AstraZeneca has developed a β-secretase 1 inhibitor (BACE-inhibitor **361**); Pantoprazole **362**, is a commercial drug applied in the treatment of gastro-esophageal reflux disease; a variety of insecticides such as Sedaxane **363**; fungicides such as Isopyrazam **364**, Benzovindiflurpyr **365**, Fluzapyroxad **366**; and agrochemicals such as Bixafen **367**, Thiazopir **368**, etc., all possess a $CF_2H$ motif in their structures, as described in Figure 3.1. Traditionally, difluoromethylated compounds have mainly been synthesised via deoxyfluorination of aldehydes with highly reactive inorganic fluorinating reagents, such as sulfur tetrafluoride ($SF_4$),[174a] *N*,*N*-diethylaminosulfur trifluoride (DAST),[174b] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor).[174c] Nevertheless, these reactions normally perform under harsh conditions, often result in problems in functional group compatibility, and formation of hazardous HF upon contact with water.

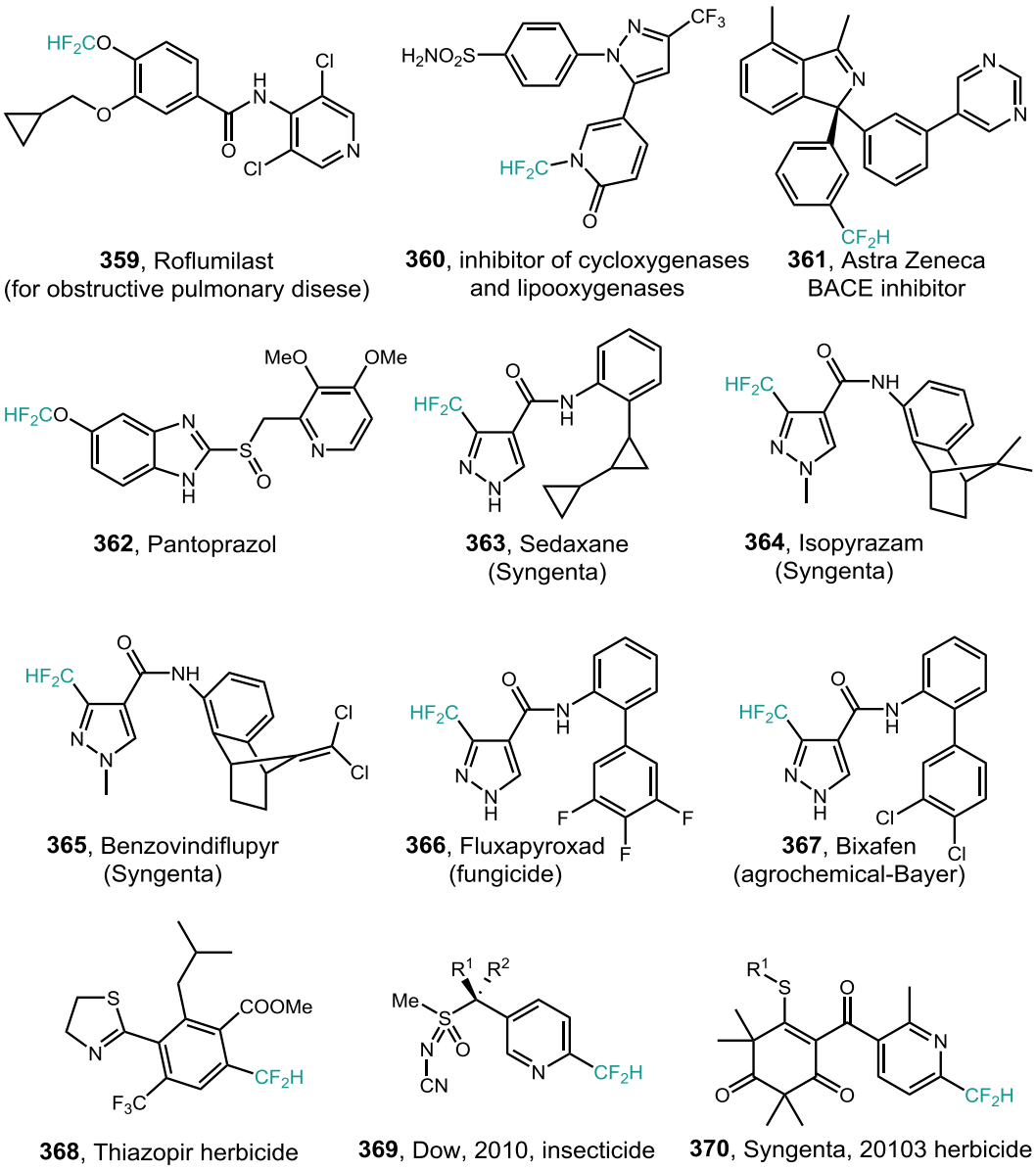
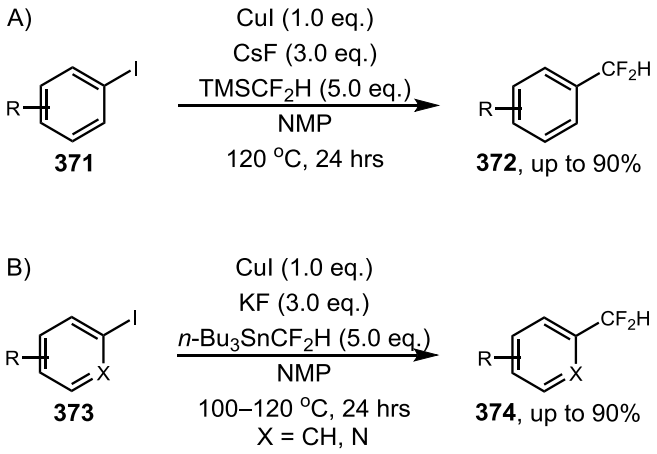



**Figure 3.1.** Difluoromethylated compounds used as therapeutic drugs, herbicides, fungicides, agrochemicals.

In addition to the early reagents, a variety of methodologies for direct difluoromethylation, such as the difluoromethylation reactions with aromatics, alkenes, alkynes and alcohols, have been intensively explored and studied, which are summarised below.

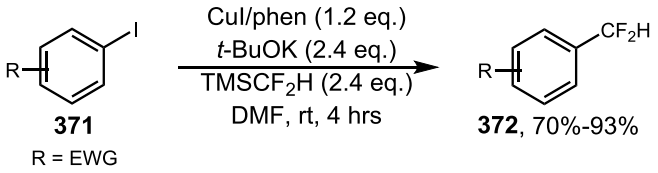
### 3.1.1. Direct Difluoromethylation of Aromatics

In 2012, Hartwig and coworkers successfully developed a straightforward method for the cross-coupling reaction of aryl iodides with commercially available, stable reagent, trimethylsilyl difluoromethane ($TMSCF_2H$).[175] The aryl iodides undergoes copper-mediated (CuI) nucleophilic difluoromethylation with generation of intermediate $Cu(CF_2H)_2^-$ smoothly, affording the $CF_2H$ substituted arenes in excellent yields; the substrate scope can be extended to vinyl iodides (see §.3.1.2) producing the corresponding products in moderate yields (Scheme 3.1A).[175] Nevertheless, the method requires significantly excessive use of $TMSCF_2H$, and is limited to electron-rich and electron-neutral iodoarenes; additionally, the reaction also encounters difficulties in compatibility with aldehydes and ketones due to competitive nucleophilic addition to carbonyl centre.[175]



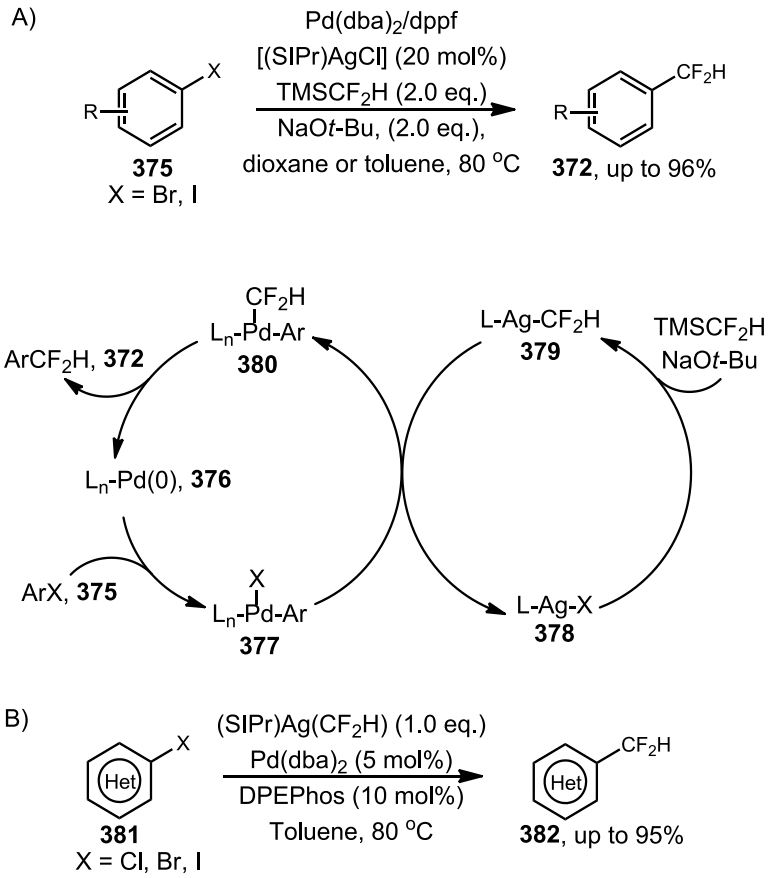

**Scheme 3.1.** Copper-mediated difluoromethylation of (hetero)aryl iodides.

Subsequently, Prakash and coworkers reported the copper-mediated difluoromethylation of (hetero)aryl iodides using *n*-$Bu_3SnCF_2H$ (Scheme 3.1B).[176] This method was proved to be effective with both activated and deactivated iodoarenes and iodoheteroarenes, and also addressed the compatibility problems with carbonyl compounds. The desired products were obtained in moderate to good yields, and the reactions with β-styryl halides also proceeded to give the corresponding products in good to excellent yields.[176] In spite of the broader scope and high efficiency, the toxicity and less accessibility of *n*-$Bu_3SnCF_2H$ limited its academic and industrial application.[176]




**Scheme 3.2.** Copper-mediated difluoromethylation of electron-deficient aryl iodides.

Alternatively, Qing and coworkers developed a new methodology, which overcome both the substrate limitation and reagent toxicity (Scheme 3.2).[177] In this process, $TMSCF_2H$ was chosen as the $CF_2H$ source, the reaction was performed under optimised conditions. Compared with Hartwig's method, less amount of $TMSCF_2H$ was required in the reaction, and addition of *N*-ligand (phenanthroline) was necessary to ensure high yields.[177] Moreover, strong base *t*-BuOK was used in place of weak base CsF, and the reaction can be carried out at room temperature rather than an elevated temperature (120 $^oC$). With all these modifications, the substrates with electron-withdrawing groups proceeded smoothly to afford the difluoromethylated arenes in good to excellent yield.[177]

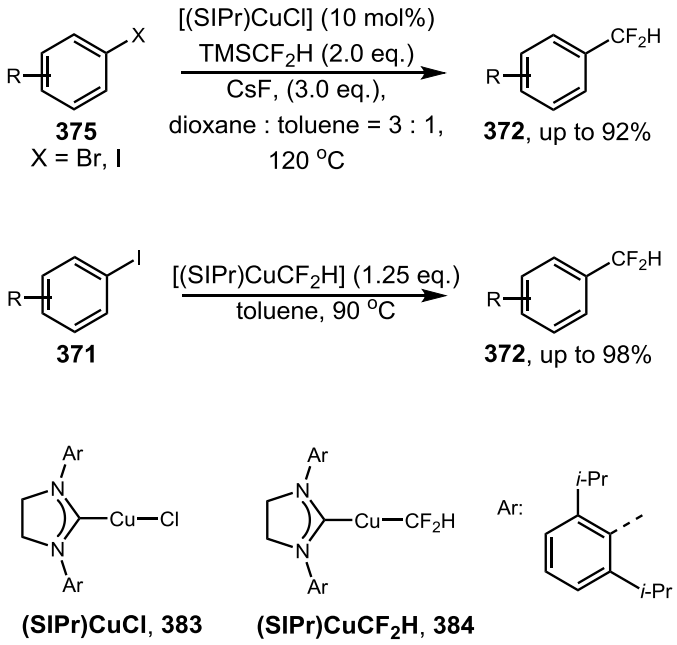



**Scheme 3.3.** Palladium-catalysed difluoromethylation of (hetero)aryl halides.

For all above methods, stoichiometric amount of metal is required. Recently, the transition metal catalysed difluoromethylation reactions have been developed.[178-180] In 2014, Shen and coworkers published the direct difluoromethylation of aryl bromides and iodides with dual palladium/silver catalyst (Scheme 3.3A).[178] Pd (0) catalyst **376** could be converted into Pd (II) complex **377** via oxidation addition to aryl halide **375**. Further transmetalation with silver complex **379**, which was generated from reaction of silver catalyst **378** and $TMSCF_2H$, afforded Pd (II) complex **380**. The final reductive elimination of complex **380** led to the formation of desired product **372** and regeneration of Pd (0) catalyst **376** (Scheme 3.3A).[178] The Pd/Ag bimetallic catalyst system cooperatively catalysed the difluoromethylation of a broad range of aryl bromides and iodides. The reaction showed great tolerance to substrates with electron-withdrawing or electron-donating groups, as well as wide compatibility with various functionalities. The powerful efficiency of this methodology is showcased by the successful difluoromethylation of three drug-like candidates.[178] This methodology provides an opportunity of accelerating the discovery of a lead compound. (Scheme 3.3A)[178]

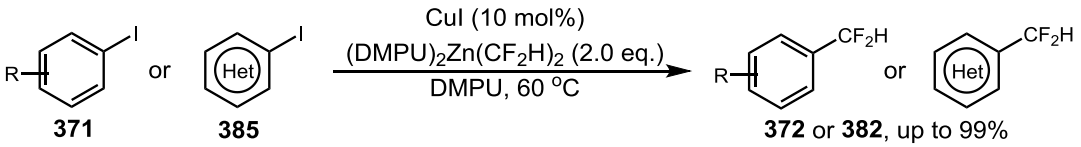
A limitation of the dual catalyst system lies in its inefficiency to heteroaryl halides. Recently, Shen and coworkers overcame this limitation by employing 1.0 equivalent of pre-made (SIPr)Ag($CF_2H$) and replaced the dppf ligand with DPEPhos. With these modifications, the reaction proceeded smoothly with heteroaryl halides, producing the corresponding products with a broad scope and generality (Scheme 3.3B).[179]

Sanford and coworkers successfully developed another NHC ligated metal complex, copper complex **384** (Scheme 3.4).[180] The copper reagent was also effective in difluoromethylation of aryl iodides, which can be pre-made or *in situ* generated with $TMSCF_2H$ and catalytic amount of (SI)CuCl **383**. A variety of aryl iodides with electron-donating or electron-withdrawing substituents could be employed in the reaction, affording the difluoromethylated arenes in good to excellent yields (Scheme 3.4).

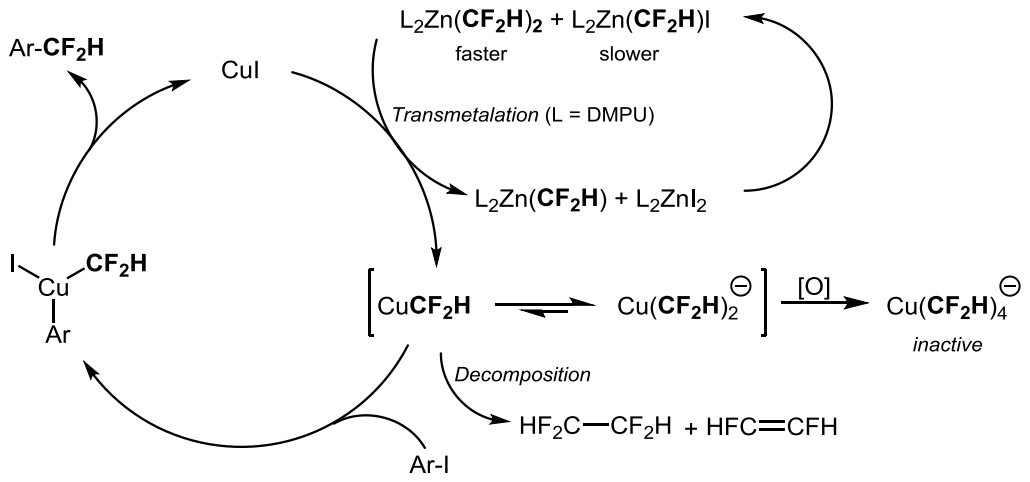



**Scheme 3.4.** Copper-catalysed difluoromethylation of aryl iodides with NHC ligand.

A disadvantage of employing of $TMSCF_2H$ as difluoromethyl source is that elevated temperatures or strong nucleophiles are required in order to cleave the strong Si-$CF_2H$ bond. An alternative reagent of choice is the difluoromethyl zinc complex.[181,182] In 2016, Mikami and coworkers successfully prepared the stable and isolatable zinc reagent $(DMPU)_2Zn(CF_2H)_2$ via reaction of difluoroiodomethane ($ICF_2H$) and zinc dust or diethylzinc in the presence of DMPU ligand. With catalytic amount of copper iodide, the difluoromethylation reaction, using $(DMPU)_2Zn(CF_2H)_2$,[181] proceeded with electron-deficient aryl iodides to give the desired product in moderate to good yield. Heteroaryl iodides were also found to be effective in the process; whereas the electron-rich aryl iodides gave low yields (Scheme 3.5).[181]



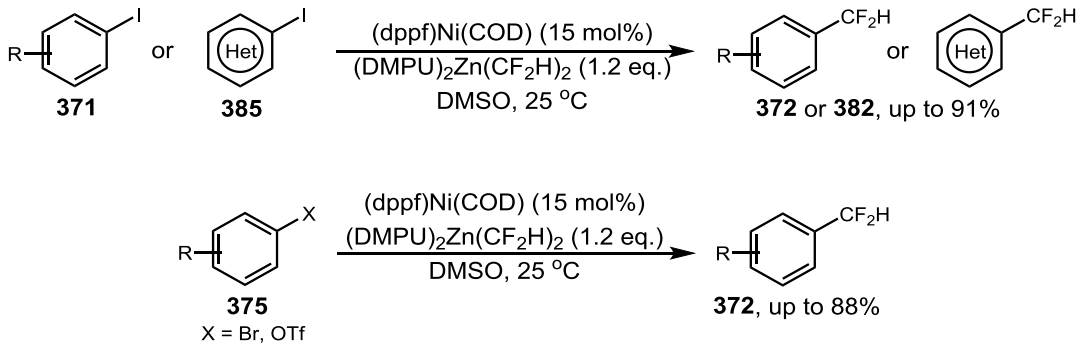

**Scheme 3.5.** Copper-catalysed difluoromethylation of aryl iodides with Zinc reagents.




**Scheme 3.6.** Mechanism of Cu-catalysed difluoromethylation of aryl iodides with Zinc reagents.

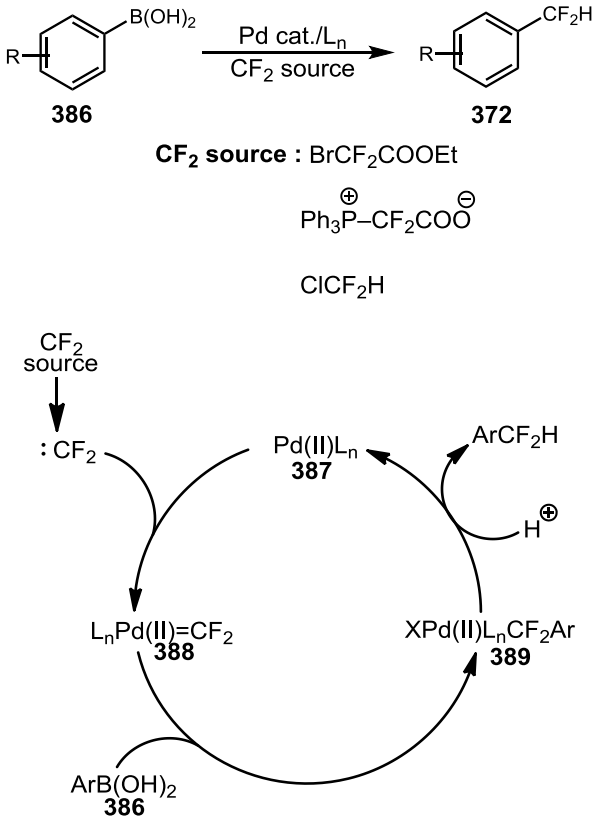
In regard to the reaction mechanism, transmetalation of the difluoromethyl group from zinc reagent to CuI initially triggers the reaction to generate neutral $CuCF_2H$ that is in equilibrium with more stable cuprate [$Cu(CF_2H)_2^-$]. Subsequently, the reaction of $CuCF_2H$ with aryl iodide results in oxidative addition (O.A.) of C-I bond with formation of copper (III) species. The final reductive elimination (R.E.) of copper (III) species led to the formation of difluoromethylated arene and regenerate the CuI catalyst, closing the catalytic cycle. Notably, the O.A. step of electron-rich substrate is relatively slow, and consequently led to the decomposition of $CuCF_2H$, producing $HF_2C$-$CF_2H$ and HFC=CFH, thus affording the desired product in low yield (Scheme 3.6).[181]

Meanwhile, Vicic and coworkers developed nickel catalysed direct difluoromethylation of aryl halides also with difluoromethyl zinc reagent independently (Scheme 3.7).[182] Under the catalysation of Ni reagent, the reaction of (hetero)aryl iodides and bromides with $(DMPU)_2Zn(CF_2H)_2$ proceeded smoothly to yield the difluoromethylated products in moderate to good yields.[182] Likewise, aryl halides with electron-donating groups were also found to be less efficient in reaction process. It is noteworthy that the reaction can be performed under rather mild conditions, and room temperature other than elevated temperature is sufficiently enough (Scheme 3.7).



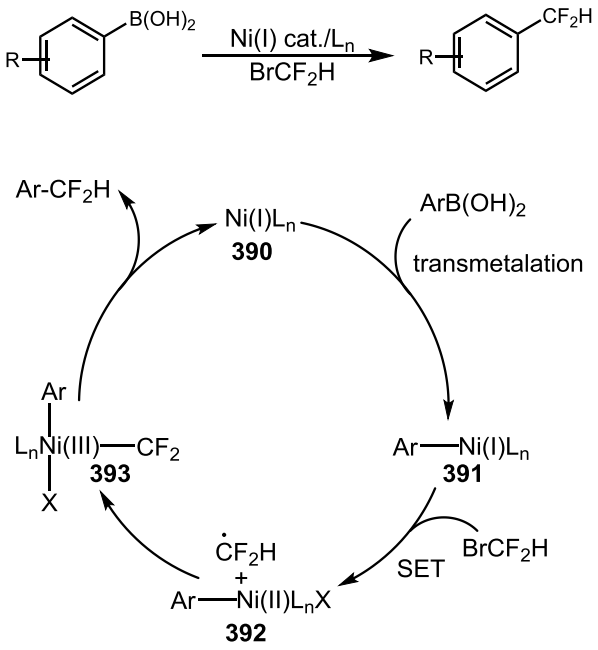

**Scheme 3.7.** Ni-catalysed difluoromethylation of aryl iodides with Zinc reagents.

In addition to aryl halides, the difluoromethylation of aryl boronic acid has also been intensively developed, with transition metals, such as palladium[183-185] and nickel,[186-188] as the reaction catalysts. Palladium catalysed reaction was initiated by the formation of Pd-carbene **388** from the reaction of Pd-catalyst **387** and *in situ* generated difluorocarbene (Scheme 3.8). Palladium (II) **388** was subsequently trapped by aryl boronic acid **386**, producing the key intermediate **389**, which, after protonolysis, afforded the desired product with the regeneration of Pd catalyst **387** (Scheme 3.8).




**Scheme 3.8.** Pd-catalysed difluoromethylation of aryl boronic acids.

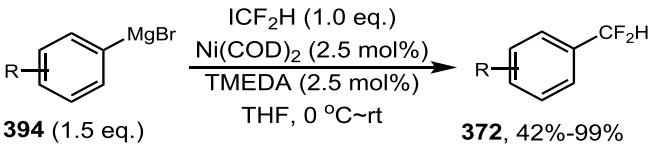
Recently, the Ni-catalysed Suzuki-Miyaura reactions have been successfully developed.[185-188] $BrCF_2H$ could serve as the difluoromethyl source. The key intermediate **392** & **393** was generated from the reaction of $BrCF_2H$ and complex Ar-Ni(I)$L_n$ **391** via single electron transfer mechanism. Finally, reductive elimination of complex **393** the difluoromethylated arene (Scheme 3.9). In general, aryl boronic acids bearing both electron-donating and electron-withdrawing substituents all showed good reactivity towards $BrCF_2H$, providing the corresponding difluoromethylated arenes in good to excellent yields. This is in sharp contrast to previous nickel catalysed nucleophilic difluoromethylation of aryl iodides, in which electron-rich aryl iodides led to no or low yields.




**Scheme 3.9.** Ni-catalysed difluoromethylation of aryl boronic acids.

In 2018, Mikami and coworkers successfully developed a conventional Ni-catalysed Kumada-Tamao-Corriu cross coupling reaction using organomagnesium Grignard reagents and difluoroiodomethane.[189] The authors pointed out that Ni(0)/Ni(II) catalytic cycle rather than the previously reported Ni(I)/Ni(III) cycles was established. Various kinds of organomagnesium reagents bearing either electron-donating or electron-withdrawing substituents can proceed smoothly to give the corresponding products in good to high yields under mild conditions (Scheme 3.10).[189] In the same year, Zhang

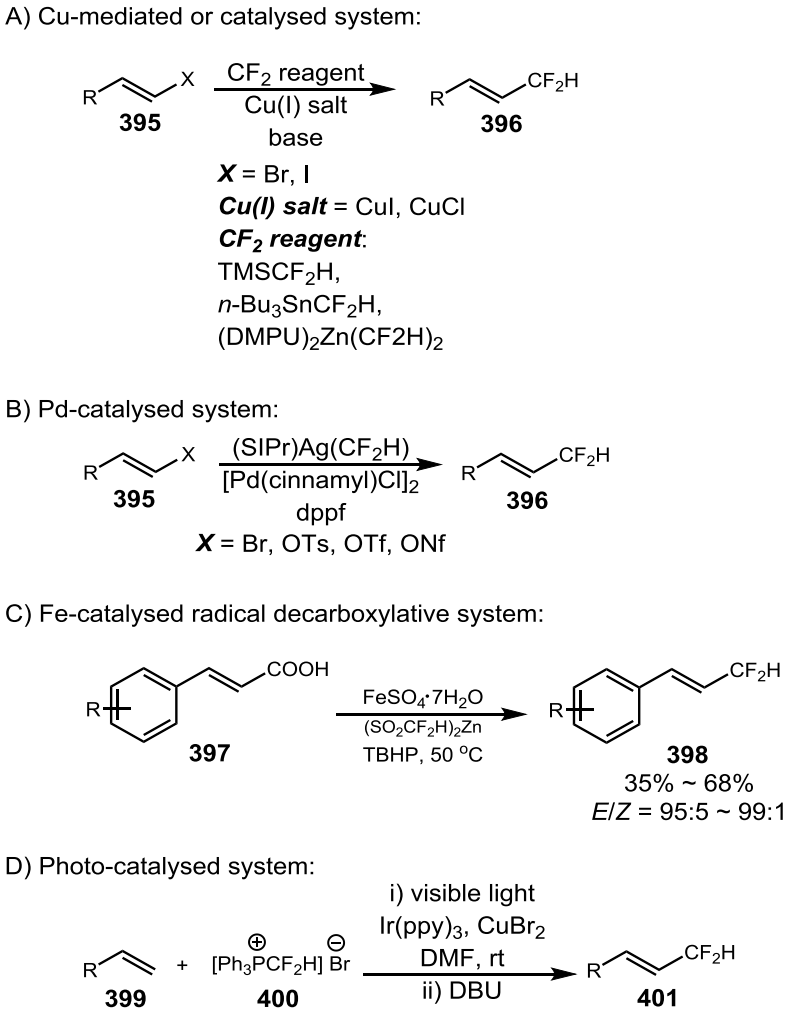
and coworkers reported the Ni-catalysed difluoromethylation of (hetero)aryl magnesium Grignard reagents, which was indicated to proceed via a radical pathway.[189]




**Scheme 3.10.** Ni-catalysed Kumada-Tamao-Corriu cross coupling reactions.

### 3.1.2. Direct Difluoromethylation of Alkenes

Due to the similar steric and electronic properties, fluoroalkylated alkenes are potentially an alternative to a peptide bond in peptidomimetics to improve bioactivity.[190-193] Therefore, difluoromethylated alkenes can serve as a valuable structural motif in drug discovery. In contrast to the remarkable progress in difluoromethylation of arenes,[166-180] the methodologies for the synthesis of difluoromethylated alkenes are less explored. Difluoromethylated alkenes are mainly prepared by difluoromethylation of functionalised alkenes. Vinyl halides can be difluoromethylated by nucleophilic reagents ($TMSCF_2H$, $n$-$Bu_3SnCF_2H$, $(DMPU)_2Zn(CF_2H)_2$) under the mediation or catalysation of copper(I) salt via the formation of $CuCF_2H$ intermediate (Scheme 3.11A).[175-177] In 2015, Shen and coworkers successfully accomplished the palladium catalysed difluoromethylation of more readily available vinyl bromides and vinyl sulfates (triflates, nonaflates, and tosylates) using NHC ligated difluoromethyl silver reagent (SIPr)Ag ($CF_2H$) (Scheme 3.11B).[194] Liu and coworkers reported the decarboxylative difluoromethylation of carboxylic acids with $(CF_2HSO_2)_2Zn$, which occurs via a radical process affording the difluoromethylated alkenes in moderate yields and excellent *E*/*Z* ratio (Scheme 3.11C).[195] Recently, Qing and coworkers published the photo-catalysed difluoromethylation of alkenes via a bromodifluoromethylation and dehydrobromination, with high yields and good *E*/*Z* selectivity (Scheme 3.11D).[196]

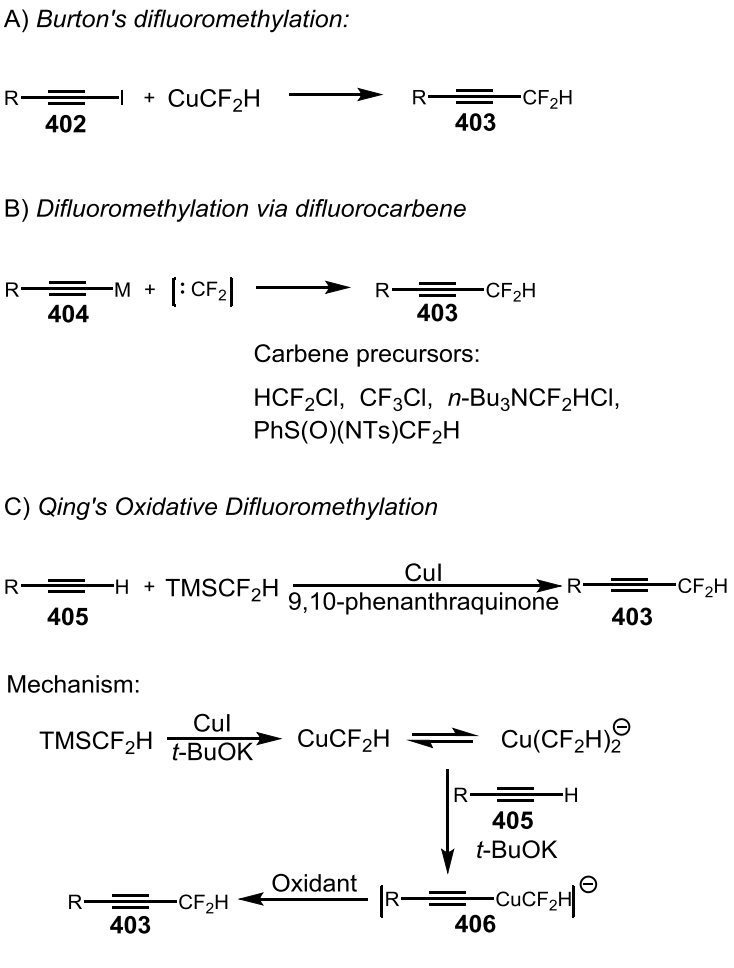



**Scheme 3.11.** Difluoromethylation of functionalised alkenes.

### 3.1.3. Direct Difluoromethylation of Alkynes

Fluorinated alkynes constitute a type of valuable building blocks due to the unique properties of fluorine atoms or fluorinated groups,[197-200] amongst them, difluoromethylated alkynes are of importance. Whilst the direct synthesis of trifluoromethylated alkynes has progressed tremendously,[201-205] the direct synthesis of the analogous difluoromethylated alkynes are less developed. There are there types of strategies to realise the direct synthesis, as depicted in scheme 3.12. Burton and coworkers reported the cross coupling reaction of 1-iodoalkynes and *in situ* generated instable $CuCF_2H$ reagent, which requires the pre-functionalisation of terminal alkynes (Scheme 3.12A).[206] Additionally, the difluoromethylation can occur via reaction of deprotonated terminal alkynes and difluorocarbene generated from various

difluorocarbene precursors (e.g. $CF_2HCl$,[207] fluoroform,[208] difluoromethyltri(*n*-butyl)ammonium chloride,[209] and difluoromethylated sulfoximine,[210] scheme 3.12B). Nevertheless, this methodology has met some difficulties with some sensitive functionalities. Moreover, the oxidative difluoromethylation of terminal alkynes in the presence of copper salt have been successfully developed by Qing and coworkers (scheme 3.12C).[211] Initially, the difluoromethyl copper species was generated and then reacted with alkyne **405** to form intermediate **406**. Subsequently, intermediate **406** was oxidised to copper (III) complexes, which finally underwent the reductive elimination to afford product **403** (Scheme 3.12C).[211]



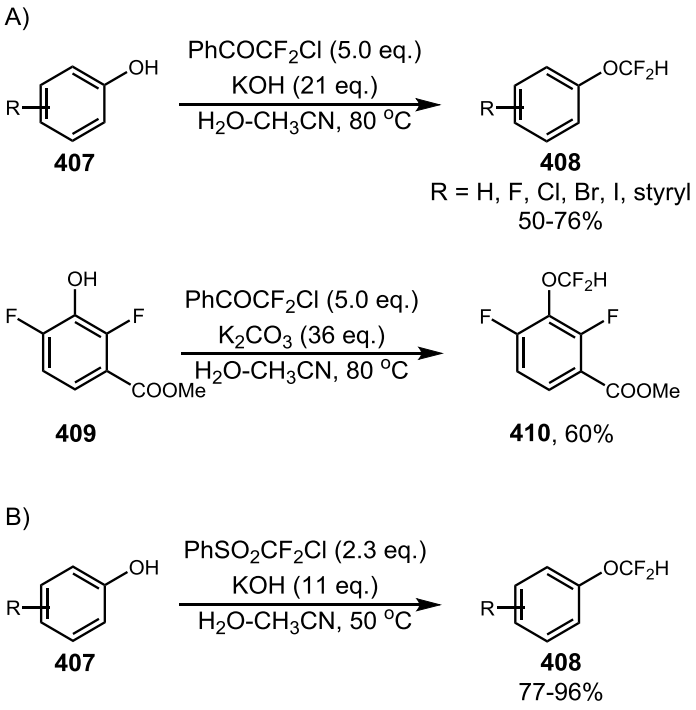

**Scheme 3.12.** Direct difluoromethylation of alkynes.

### 3.1.4. Direct Difluoromethylation of Phenols and Alcohols

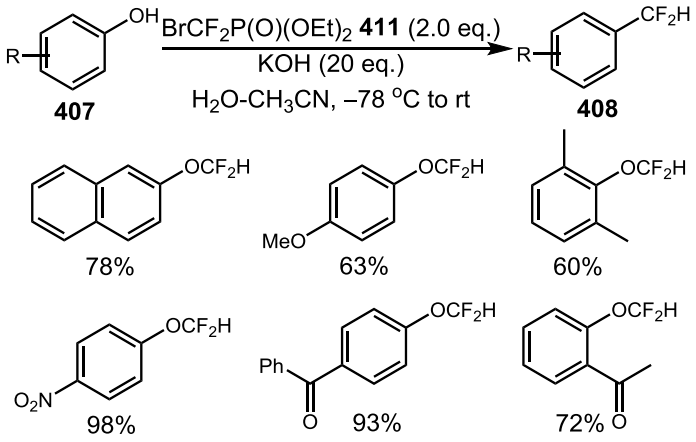
In addition to difluoromethylation of carbon atoms, the difluoromethylation reactions of heteroatoms (e.g. O, S and N) have also been extensively explored.[212] During the past decades, great effort has been made to realise the synthesis of difluoromethyl ethers.[213,214] The most commonly utilised strategies are difluoromethylation of alcohols and phenols with difluorocarbene ($:CF_2$).

Amongst all available methods, the reaction between chlorodifluoromethane ($HCF_2Cl$) and phenols under basic conditions is the most commonly utilised one.[215-218] Chlorodifluoroacetates ($ClCF_2COONa$, or $ClCF_2COOMe$) are also effective reagents for difluoromethylation of phenols.[219-221] Alternatively, a series of reagents, such as $CF_2Br_2$,[222] $HCF_2Br$,[223] $CF_3COONa$,[224] $FSO_2CF_2COOH$,[225] $CF_3ZnBr$,[226] have also been developed to accomplish the synthesis of difluoromethyl ethers from phenols; however, their applications are limited due to their low productivity and/or difficult availability. Moreover, the use of chlorodifluoromethane is also regulated since it is a ozone depleting substance. As a result, alternative efficient and easily accessible reagents are of great demand.

In 2006, Hu and coworkers accomplished the synthesis of difluoromethyl ethers using excess of $PhCOCF_2Cl$ and phenols under aqueous basic conditions.[227] Difluorocarbene was firstly generated from the reaction of $PhCOCF_2Cl$ with KOH and subsequent α-elimination of chlorodifluoromethyl anion; further reactions with various substituted phenols yielded desired ethers in good yields (Scheme 3.13). Base-sensitive functionality can be tolerated by the use of weaker base (Scheme 3.13A).[227] Later, Hu and coworkers found that sulfone $PhSO_2CF_2Cl$ was also an effective reagent for difluoromethylation of phenols (Scheme 3.13B).[228] Comparatively, the base-promoted $SO_2$-$CF_2Cl$ bond cleavage is slower than that of $CO_2$-$CF_2Cl$ bond, resulting in a more controllable formation of difluorocarbene.[228] Thus, the amount of sulfone is substantially decreased. The reactions proceeded effectively with both electron-rich and electron-deficient phenols (Scheme 3.13B).



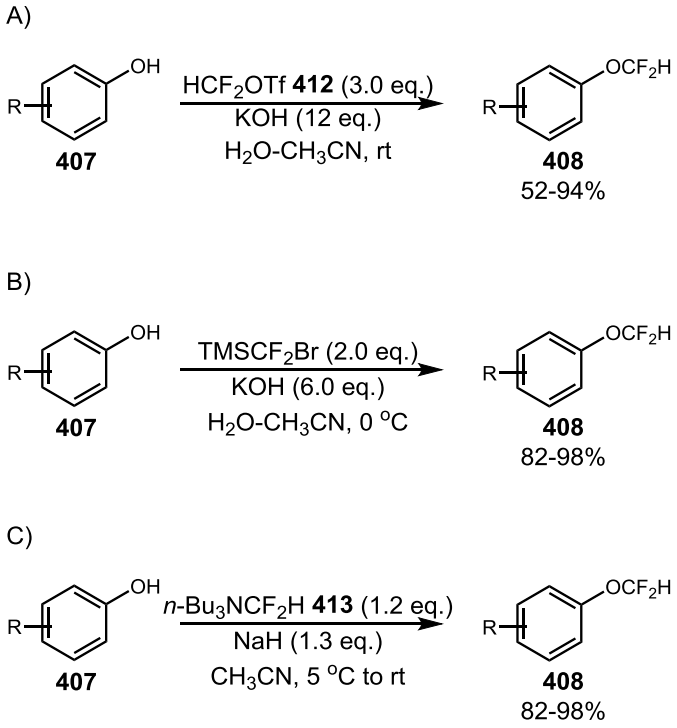

**Scheme 3.13.** Difluoromethylation of phenols with 2-chloro-2,2-difluoroacetophenone and chlorodifluoromethyl phenyl sulfone.




**Scheme 3.14.** Difluoromethylation of phenols with diethyl bromo difluoromethylphosphonate.

In 2009, Zafrani and coworkers reported an efficient and eco-friendly difluorocarbene precursor phosphonate **411** (Scheme 3.14),[229] which underwent facile P-C bond cleavage under basic conditions at low temperature (–78 °C to rt), after decomposition of *in situ* generated bromodifluoromethyl anion, leading to formation of difluorocarbene. The reaction showed great compatibility with a variety of functional groups, including enolisable carbonyl group (Scheme 3.14).[229]

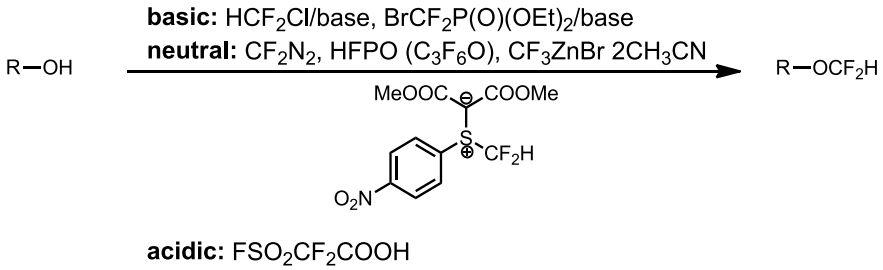
Additionally, other easily accessible reagents, such as $HCF_2OTf$,[230] $TMSCF_2Br$,[231] and *n*-$Bu_3N(HCF_2)Cl$,[209] have also been disclosed as efficient reagents for the difluoromethylation of phenols under mild conditions (Scheme 3.15). Hartwig and coworkers reported that $HCF_2OTf$ can be employed in difluoromethylation reactions with a wide array of phenols, demonstrating a broad functional group tolerance (Scheme 3.15A).[230] Commercially available $TMSCF_2Br$ was exploited in the synthesis of aryl difluoromethyl ethers by Hu and coworkers (Scheme 3.15B); its reaction with phenols can be conducted with much less KOH compared with similar reactions using phosphonate **411** or difluoromethyl triflate **412**, showing high efficiency with phenols bearing both electron-donating and electron-withdrawing substituents (Scheme 3.15B).[231] Desired products can be effectively afforded in moderate to excellent yields with only slightly excess of ammonium chloride **413** and base in organic solvent-$CH_3CN$ (Scheme 3.15C).[209]




**Scheme 3.15.** Difluoromethylation of phenols with $HCF_2OTf$, $TMSCF_2Br$, and *n*-$Bu_3N(HCF_2)Cl$.

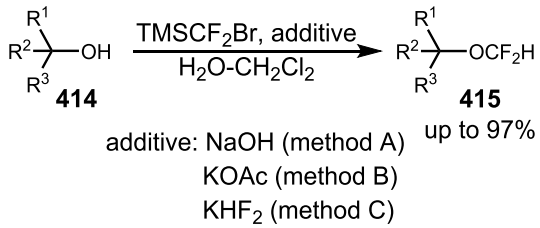
The difluoromethylation of alcohols under similar basic conditions is normally less effective due to the competitive side reactions caused by the base. To date, few reagents,

such as $HCF_2Cl$,[232,233] and $BrCF_2P(O)(OEt)_2$,[234] have been reported for difluoromethylation of alcohols under basic conditions with limited functionality tolerance (Scheme 3.16, basic). Some alternative approaches that can avoid strongly basic conditions with special difluorocarbene precursors, such as $CF_2N_2$,[235] HFPO,[236] $CF_3ZnBr{\cdot}2CH_3CN$,[237] and difluoromethylated sulfonium ylide,[238] have been exploited for alcohol difluoromethylation. However, these methods usually require excess amounts of alcohols and suffer from narrow substrate scope (Scheme 3.16, neutral). A modification of Chen's method has resulted in an effective difluoromethylation of primary and secondary alcohols with $FSO_2CF_2CO_2H$ (Scheme 3.16, acidic);[239] however, the reaction with tertiary alcohols remains challenging. Furthermore, the release of $SO_2$, an air pollutant, as a byproduct may limit its wide application.




**Scheme 3.16.** Available methods for difluoromethylation of alcohols.

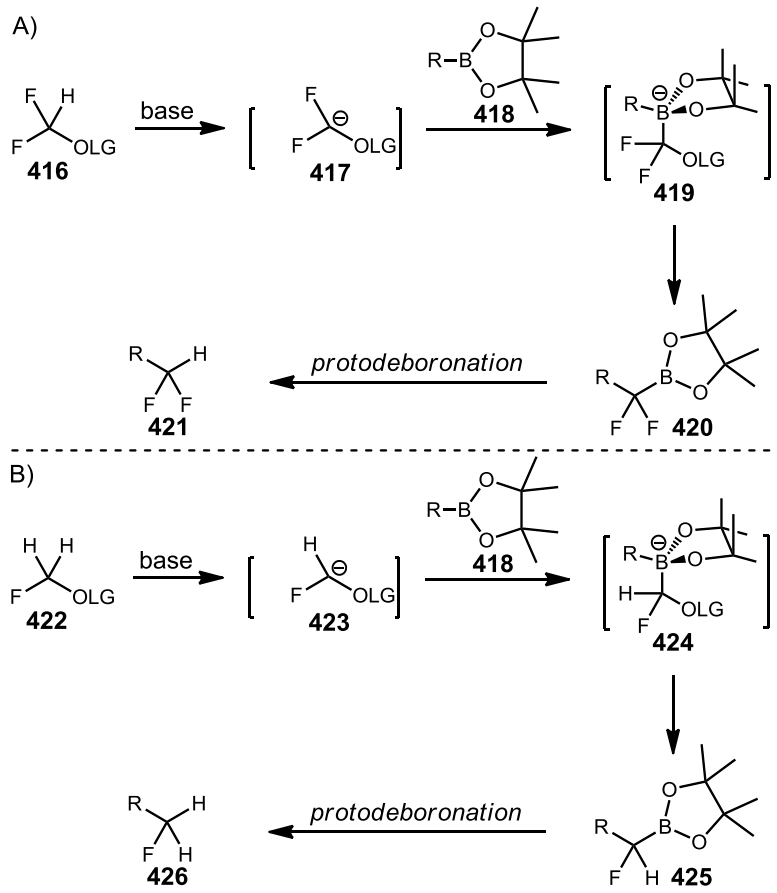
Hu and coworkers accomplished a convenient difluoromethylation of alcohols using $TMSCF_2Br$, which allows primary, secondary, and tertiary alkyl difluoromethyl ethers to be synthesised via simple procedures (Scheme 3.17).[240] The reaction proceeds through direct interaction between neutral alcohol and difluorocarbene, a different mechanism from the difluoromethylation of phenols.[240]




**Scheme 3.17.** Difluoromethylation of tertiary alcohols $TMSCF_2Br$.

### 3.1.5. Project Aims

Despite the remarkable progress of difluoromethylation reactions, the difluoromethylation of unactivated carbon centres remains largely undeveloped. To achieve this aim, the lithiation–borylation methodology can be a suitable strategy. We proposed that difluoromethylated reagent **416**, with a suitable leaving group (LG), could be deprotonated with base to generate anion **417**, which can subsequently react with boronic ester **418**, leading to the formation of boronate complex **419** (Scheme 3.18A). Finally, 1,2-metalate rearrangement at elevated temperature and protodeboronation[86-88] will afford the difluoromethylated alkane **421** (Scheme 3.18A). This strategy could also provide an opportunity to synthesise chiral difluoromethylalkanes, which are normally prepared with low enantioselectivity using existing methods, by employing enantioenriched boronic esters.[241] Additionally, the monofluoromethylation reactions via lithiation–borylation methodology was also proposed (Scheme 3.18B).




**Scheme 3.18.** Proposed strategy of difluoromethylation of un-activated carbon centres.

## 3.2. Initial Explorations and Outlook

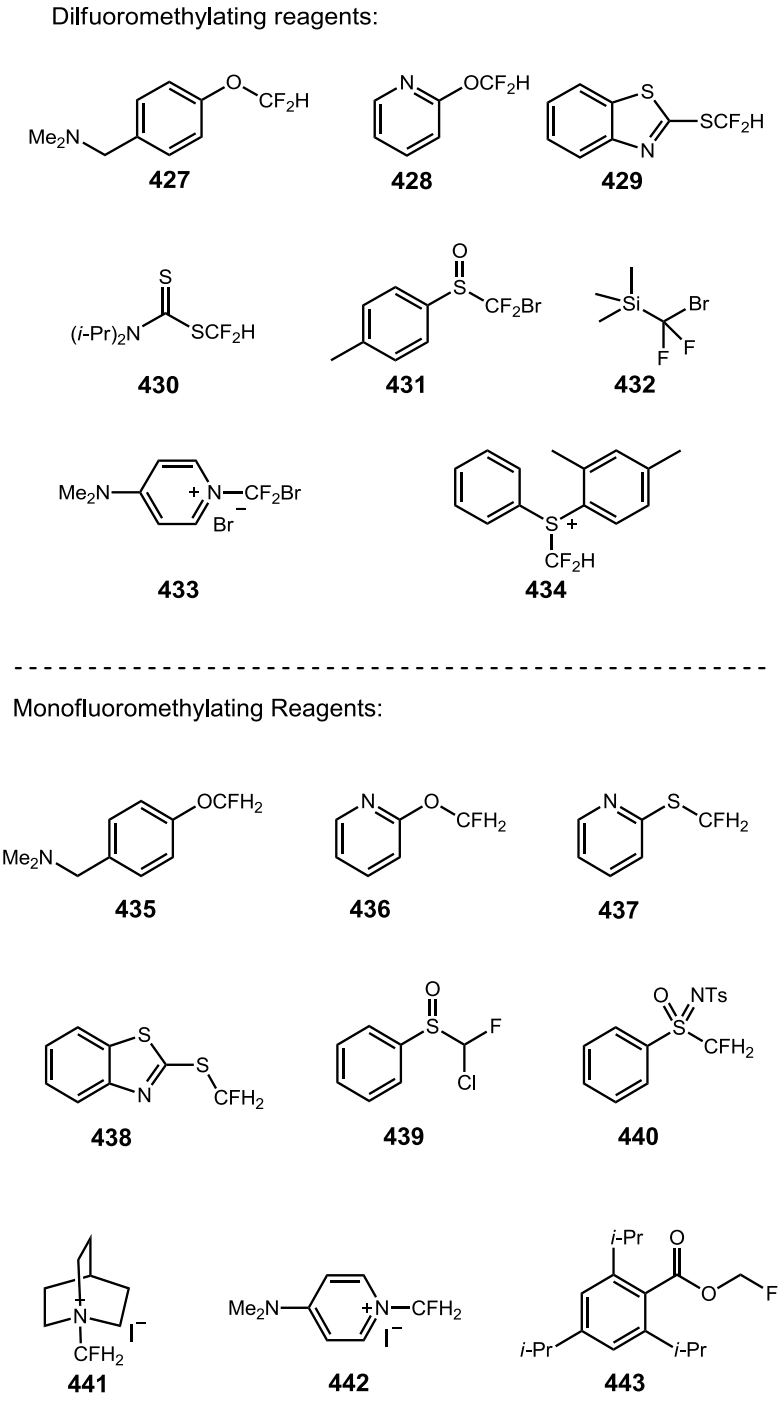
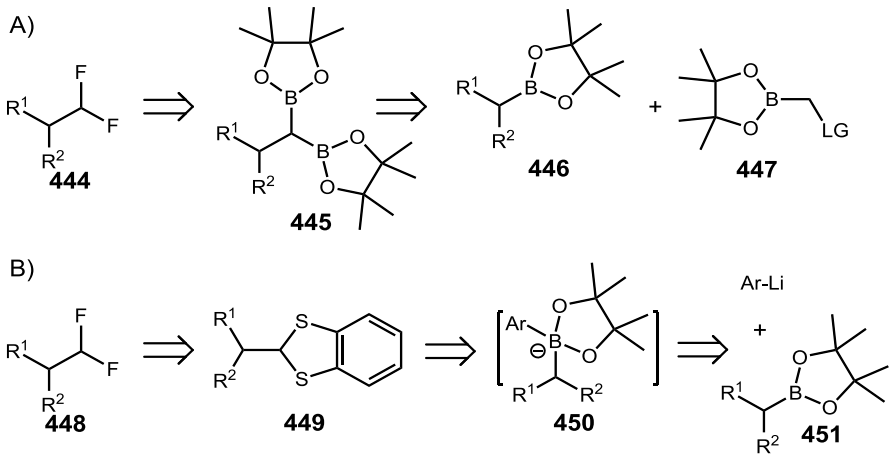



**Figure 3.2.** Difluoromethylating and monofluoromethylating reagents.

Based on the aboved ideas, we carried out extensive exploration into this project, a variety of fluorinating reagents were synthesised and investigated, which are

summarised in Figure 3.2. Unfortunately, all attempts did not afford any desired product, which probably resulted from the instability of the generated carbenoid **417** or **423**, which can easily decompose and form fluorinated carbene. The formation of the boronate complex, a key intermediate, was never detected.

To accomplish the difluoromethylation or monofluoromethylation reactions, different strategies should be exploited. Due to the instability of fluorinated carbenoid, the subsequent boronate complex cannot be formed. As a result, we should avoid the step of fluorinated 'ate' complex formation. Two possibly feasible strategies can be utilised: difluoromethyl alkanes could be generated via fluorination of diboronic esters (Scheme 3.37A) or dithio-compound (Scheme 3.37B). The former can be synthesised from the lithiation–borylation of boronic ester **446** and boronic ester **447**, while the latter can be prepared via the reaction of boronate complex and electrophiles (Scheme 3.19).




**Scheme 3.19.** Outlook for new strategies for difluoromethylation reactions.

# 4. Experimental

## *4.1. General Experimental*

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under nitrogen atmosphere using standard Schlenk manifold technique. Analytical TLC was performed on aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualised by exposure to UV-light or stained using $KMnO_4$, anisaldehyde or phosphomolybdic acid (PMA) followed heating. Flash column chromatography was performed using Sigma Aldrich silica gel 60 (40-60 µm). All mixed solvent eluents are reported as v/v solutions.

All required fine chemicals were purchased from Acros Organics, Alfa Aesar, Inochem-Frontier Scientific, Sigma-Aldrich, TCI Europe or Santa Cruz Biotechnology and used as received unless otherwise mentioned. *n*-Butyllithium and *s*-Butyllithium were received from Acros Organics as 1.6 M solution in hexane or 1.3 M solution in cyclohexane/hexane. Anhydrous DMF was purchased from Acros Organics and used as received. Anhydrous $CH_3CN$, $CH_2Cl_2$, diethyl ether, THF and toluene were obtained from a purification column composed of activated alumina and stored subsequently over 3Å molecular sieves.

$^1H$, $^{13}C$, $^{11}B$, $^{19}F$ Nuclear magnetic resonance (NMR) spectra were acquired using Joel ECS 300, Joel ECS 400, Bruker 400, Varian 400 or Varian 500 spectrometer in Chloroform-d, Methanol-$d_4$ or DMSO-$d_6$ at 300, 400 or 500 MHz as indicated. $^1H$ NMR Chemical shifts are expressed in parts per million (ppm) and referenced internally to the residual non-deuterated solvent signal. $^1H$ NMR coupling constants are expressed in hertz (Hz) and are referred to apparent multiplicities (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = doublet of doublet etc.). $^{13}C$ NMR spectra were recorded at 101 or 126 MHz, and chemical shifts ($\delta_C$) are expressed in ppm. $^{11}B$ NMR spectra were recorded using Norell S-200-QTZ quartz tubes at 128 MHz with complete proton decoupling, and chemical shifts ($\delta_B$) are

expressed in ppm. $^{19}F$ NMR spectra were recorded at 376 MHz, and chemical shifts ($\delta_F$) are expressed in ppm.

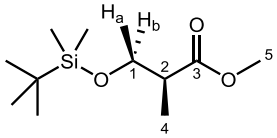
Mass spectra were recorded by the departmental mass spectrometry service of the University of Bristol, School of Chemistry, using electron impact ionisation (EI) or electrospray ionisation (ESI) techniques for high-resolution mass spectra. HRMS ESI was performed on either a Bruker Daltonics Apex IV, 7-Tesla FT-ICR or micro TOF II. Samples were submitted in EtOAc, $CH_2Cl_2$ or $CHCl_3$.

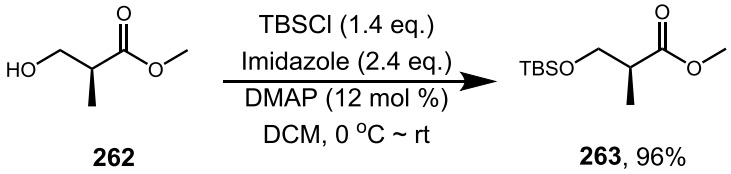
All infrared (IR) spectra were recorded on the neat compounds using a Perkin-Elmer Spectrum One FT-IR spectrometer, irradiating between 4000 $cm^{-1}$ and 600 $cm^{-1}$. Only strong and selected absorbances ($\nu_{max}$) are reported.

Optical rotations were measured on Bellingham and Stanley Ltd. ADP220 polarimeter. Melting point ranges were determined with a Kofler hot-stage apparatus and reported uncorrected.

## 4.2. Experimental Section

**methyl (*S*)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate (263)**





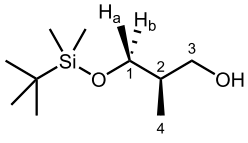

**262** **263**, 96%

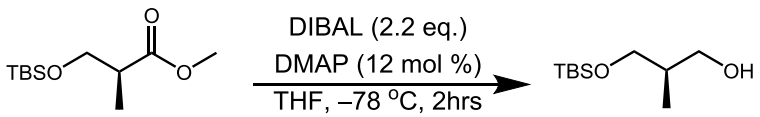
A solution of (*S*)-Roche ester **262** (5.0 g, 42 mmol), DMAP (0.1 g, 5.2 mmol), imidazole (6.90 g, 0.10 mol) in $CH_2Cl_2$ (45 mL) was cooled to 0 °C and then TBSCl (8.5 mL, 57 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 hrs before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the flask. The phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a residue that was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to give the ester **263** (9.5 g, 96%) as a colourless oil.

**$^1$H NMR** (301 MHz, Chloroform-d) δ 3.76 (dd, *J* = 9.7, 7.0 Hz, 1H, 1-$H_a$), 3.66 (s, 3H, 5-$CH_3$), 3.63 (dd, *J* = 9.7, 6.1 Hz, 1H, 1-$H_b$), 2.63 (ddq, *J* = 7.0, 6.1, 7.0 Hz, 1H, 2-H), 1.12 (d, *J* = 7.0 Hz, 3H, 4-$CH_3$), 0.85 (s, 9H, C($CH_3$)$_3$), 0.02 (s, 6H, 2 x Si-$CH_3$).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 175.4 (-C=O), 65.2 (1-C), 51.5 (2-C), 42.5 (2-C), 25.7 (*C*($CH_3$)$_3$), 18.2 (3C, C(*C*$H_3$)$_3$), 13.4 (4-C), –5.5 (2C, 2 × Si-$CH_3$).
$[\alpha]_D^{20}$ = +19 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +18.1 (c 1.1, $CHCl_3$)].

All analytical data is consistent with that previously reported.[243]

**(*R*)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropan-1-ol (264)**






**263** **264**, 92%

To a solution of compound **263** (5.0 g, 21.5 mmol) in THF (47 mL) was added a solution of DIBAL (47.3 mL, 47.3 mmol, 1.0 M in hexane) dropwise at –78°C. The solution was stirred for 2 hrs at that temperature and additional 0.5 hr at room temperature. After that, water (0.86 mL), aq. NaOH (0.86 mL, 15 %), and water (2.15 mL) were slowly added to the reaction mixture. Subsequently, the reaction mixture was allowed to warm up to room temperature and stirred for 30 min. After that anhydrous $MgSO_4$ was added and the mixture was stirred for additional 15 min, filtered over celite, and concentrated under vacuo to give a residue that was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:10) to give the alcohol **264** (4.0 g, 92%) as a colourless oil.

**$R_f$**: 0.31 (ethyl acetate : petroleum ether = 0.1)

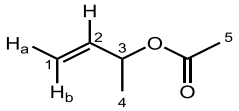
**$^1$H NMR** (400 MHz, Chloroform-d) δ 3.72 (dd, *J* = 9.9, 4.7 Hz, 1H, 1-H), 3.66 – 3.49 (m, 3H, 2 × 3-H+1-H), 2.72 (brs, 1H, OH), 1.92 (m, 2-H), 0.88 (s, 9H, 3 × C(C*H*$_3$)$_3$), 0.82 (d, *J* = 6.9 Hz, 3H, 4-$CH_3$), 0.06 (s, 6H, 2 × $CH_3$).

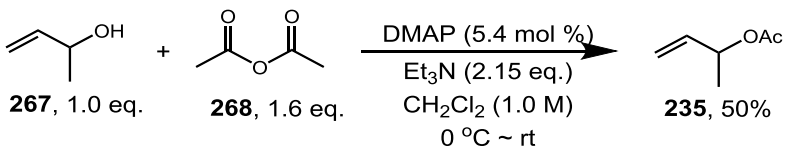
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 68.7 (1-C), 68.3 (3-C), 37.0 (2-C), 25.8 (3 × $CH_3$), 18.1 (C(*C*H$_3$)$_3$), 13.1 (4-C), –5.6 (Si-$CH_3$), –5.7 (Si-$CH_3$).

$[\alpha]_D^{20}$ = +10 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +9.79 (c 2.38, $CH_2Cl_2$)].

All analytical data is consistent with that previously reported.[244]

**but-3-en-2-yl acetate (235)**



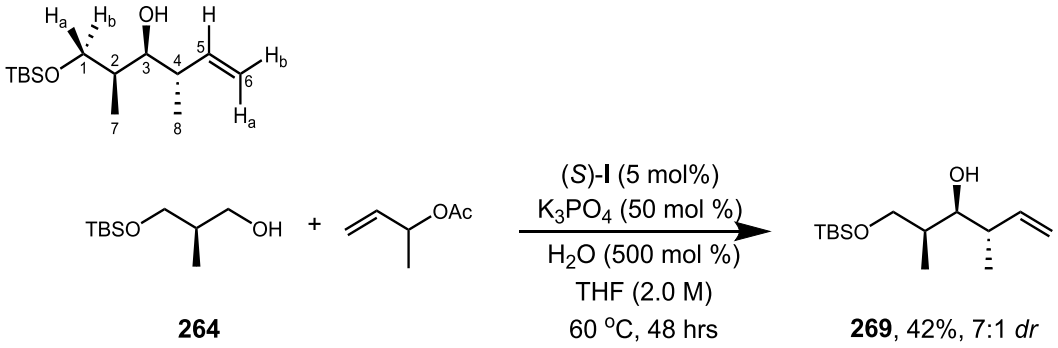

**267**, 1.0 eq. **268**, 1.6 eq. **235**, 50%

To a stirred solution of 3-butene-2-ol **267** (13.0 mL, 150.0 mmol), DMAP (1.00 g, 8.1 mmol), $Et_3N$ (45 ml, 323.0 mmol), and $CH_2Cl_2$ (150 mL) in a round bottom flask was added acetic acid anhydride **268** dropwise (23.0 mL, 242.3 mmol) at 0 °C. The reaction was allowed to warm to room temperature over 4 hrs. The reaction mixture was transferred into a separatory funnel with 70 mL 2M HCl aqueous solution. The layers were separated. The organic layer was washed once with 50 mL saturated $NaHCO_3$ aqueous solution and 50 mL of a 1:1 mixture of saturated brine and saturated $CuSO_4$ aqueous solution. The organic layer was dried with $MgSO_4$, filtered, and the volatiles were removed *via* rotary evaporation (250 mbar, 35 °C). The residue was subjected to distillation over $K_2CO_3$ (bp = 120-125 °C) to afford but-3-en-2-yl acetate **235** (8.56 g, 50% yield) as a colourless oil.

**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.84 (ddd, *J* = 17.2, 10.5, 6.5 Hz, 1H, 2-H), 5.38 – 5.29 (m, 1H, 3-H), 5.23 (dd, *J* = 17.2, 1.3 Hz, 1H, 1-$H_b$), 5.13 (dd, *J* = 10.5, 1.3 Hz, 1H, 1-$H_a$), 2.05 (s, 3H, 5-$CH_3$), 1.31 (d, *J* = 6.5 Hz, 3H, 4-$CH_3$).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 170.1 (C=O), 137.6 (Ar-C), 115.4 (Ar-C), 70.8 (3-C), 21.0 ($CH_3$), 19.8 ($CH_3$).

All analytical data is consistent with that previously reported.[245]

**(2S,3S,4S)-1-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (269)**




An oven-dried sealed tube under an atmosphere of $N_2$ was charged with **264** (102.2 mg, 0.50 mmol), (*S*)-**I** (25.8 mg, 0.025 mmol), $K_3PO_4$ (53.1 mg, 0.10 mmol), THF (0.25 mL, 2.0 M), and $H_2O$ (45 μL, 2.5 mmol). But-3-en-2-yl acetate **235** (114.1 mg, 1.0 mmol) was added and the mixture was allowed to stir at room temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 °C and was allowed to stir for

48 hrs. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (ethyl acetate : petroleum ether = 1:50) provided *syn, anti*-olefin **269** (53.5 mg, 42%) as a colourless oil.

**$R_f$**: 0.31 (ethyl acetate : petroleum ether = 1:20)

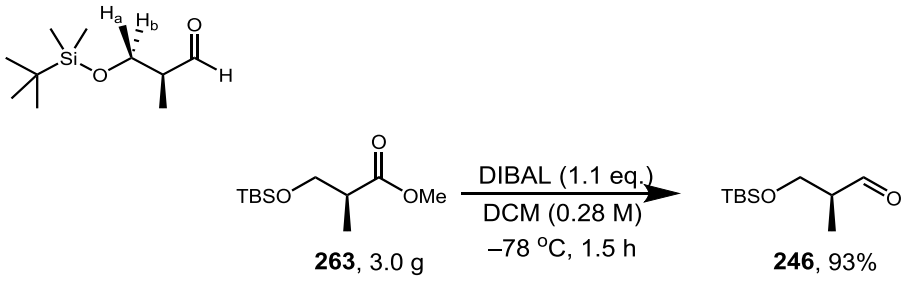
**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.82 (ddd, *J* = 17.1, 10.2, 8.3 Hz, 1H, 5-H), 5.15 – 5.03 (m, 2H, 6-$H_{a,b}$), 3.69 (m, 2H, 1-$H_{a,b}$), 3.52 (dd, *J* = 8.7, 2.4 Hz, 1H, 3-H), 2.75 (s, 1H, OH), 2.26 (m, 1H, 4-H), 1.78 (m, 1H, 2-H), 0.94 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.93 (d, *J* = 7.0 Hz, 3H, 7-$CH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.1 (5-C), 115.1 (6-C), 76.8 (3-C), 68.4 (1-C), 41.8 (4-C), 36.2 (2-C), 25.9 (3C, $C(CH_3)_3$), 18.2 ($C(CH_3)_3$), 16.6 (8-$CH_3$), 9.3 (7-$CH_3$), –5.5 (Si-$CH_3$), –5.6 (Si-$CH_3$).

$[\alpha]_D^{20}$ = –0.36 (c 0.8, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = –0.6 (c 2.6, $CHCl_3$)].

All analytical data is consistent with that previously reported.[246]

**(*S*)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanal (246)**



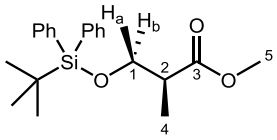

To a solution of (S)-methyl 3-(*tert*-butyldimethylsilyl)-2-methylpropanoate **263** (3.0 g, 13.1 mmol) in $CH_2Cl_2$ (46 mL) at –78 °C was added DIBAL (14.4 mL, 1.0 M in hexane, 14.4 mmol) dropwise. After being stirred for an additional 2 hrs at –78 °C, 0.58 mL of water was slowly added to the reaction mixture at –78 °C, subsequently 0.58 mL of NaOH (15% aqueous solution) was slowly added, followed by slow addition of 1.4 mL of water. Then the reaction mixture was allowed to warm up to rt and stirred for 30 min. Sequentially, anhydrous $MgSO_4$ was added and the reaction was stirred for another 15 min, filtered and concentrated under vacuo to afford aldehyde **246** without another further purification (2.5 g, 93%).

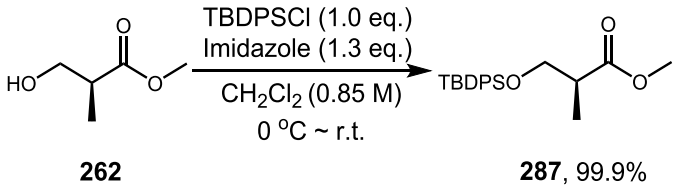
**$^1$H NMR** (400 MHz, Chloroform-d) δ 9.74 (s, 1H, CHO), 3.85 (dd, *J* = 9.9, 5.1 Hz, 1H, $CH_2$), 3.79 (dd, *J* = 9.9, 6.4 Hz, 1H, $CH_2$), 2.53 (qt, *J* = 7.0, 5.8 Hz, 1H, CH), 1.09 (d, *J* = 7.0 Hz, 3H, $CH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, 2 × Si-$CH_3$).

$[\alpha]_D^{20}$ = +33.1 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +32.5 (c 1.2, $CHCl_3$)].

All analytical data is consistent with that previously reported.[164]

**methyl (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate (287)**




**262** **287**, 99.9%

To a solution of commercially available (*S*)-Roche ester **262** (5.00 g, 42.3 mmol, 1 eq.) and imidazole (3.75 g, 55.0 mmol) in $CH_2Cl_2$ (50 mL) at 0 °C, TBDPSCl (11.08 mL, 11.6 g, 42.3 mmol) was slowly added. Then the reaction was allowed to warm up to room temperature and stirred for 20 hrs. After the reaction mixture was quenched with a saturated aqueous $Na_2CO_3$ solution (40 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuo, and purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:10) to afford ester **287** (15.1 g, 99.9%)

**$R_f$**: 0.38 (ethyl acetate : petroleum ether = 1:10)

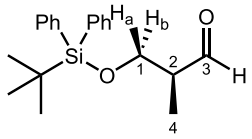
**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.76 – 7.60 (m, 4H, Ar-H), 7.49 – 7.32 (m, 6H, Ar-H), 3.83 (dd, *J* = 9.7, 6.9 Hz, 1H, 1-$H_a$), 3.73 (dd, *J* = 9.7, 5.4 Hz, 1H, 1-$H_b$), 3.69 (s, 3H, 5-$CH_3$), 2.72 (ddq, *J* = 6.9, 5.4, 7.0 Hz, 1H, 2-H), 1.16 (d, *J* = 7.0 Hz, 3H, 4-$CH_3$), 1.03 (s, 9H, $C(CH_3)_3$).

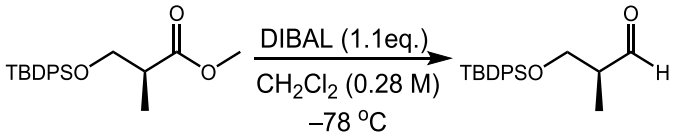
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 175.4 (-C=O), 135.6 (Ar-C), 133.5 (Ar-C), 129.6 (Ar-C), 127.6 (Ar-C), 65.9 (1-C), 51.5 (5-C), 42.4 (2-C), 26.7 (C($CH_3$)$_3$), 19.2 ($C$($CH_3$)$_3$), 13.5 (4-C).

$[\alpha]_D^{20}$ = +17 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +12.5 (c 2.6, ethyl acetate)].

All analytical data is consistent with that previously reported.[164b]

**(*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-methylpropanal (288)**




**287** **288**, 97%

To a solution of (*S*)-methyl 3-(tert-butyldiphenylsilyl)-2-methylpropanoate **287** (3.0 g, 8.5 mmol, 1.0 eq.) in $CH_2Cl_2$ (30 mL) at –78 °C was added DIBAL (9.0 mL, 1.0 M in hexane, 9.0 mmol, 1.1 eq.) dropwise over 8 min. After being stirred for an additional 6 hrs at –78 °C, 0.36 mL of water was slowly added to the reaction mixture at –78 °C, subsequently 0.36 mL of NaOH (15% aqueous solution) was slowly added, followed by slow addition of 0.9 mL of water. Then the reaction mixture was allowed to warm up to rt and stirred for 30 min. Sequentially, anhydrous $MgSO_4$ was added and the reaction was stirred for another 15 min, filtered and concentrated under vacuo to afford aldehyde **289** without another further purification (2.66 g, 97%).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 9.76 (s, 1H, CHO), 7.66 – 7.61 (m, 4H, Ar-H), 7.45 – 7.34 (m, 6H, Ar-H), 3.89 (dd, *J* = 10.3, 5.0 Hz, 1H, 1-$H_b$), 3.84 (dd, *J* = 10.3, 6.4 Hz, 1H, 1-$H_a$), 2.60 – 2.51 (m, 1H, 2-H), 1.09 (d, *J* = 7.1 Hz, 3H, 4-$CH_3$), 1.03 (s, 9H, $C(CH_3)_3$).

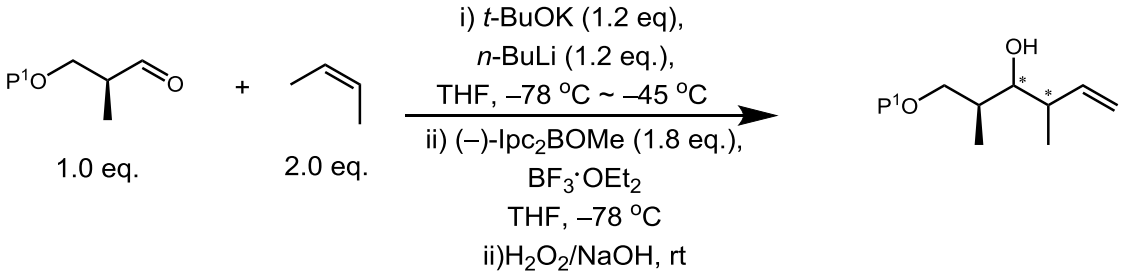
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 204.5 (C=O), 135.6 (Ar-C), 133.2 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 64.1 (1-C), 48.8 (2-C), 26.8 (3C, $C(CH_3)_3$), 19.2 ($C(CH_3)_3$), 10.3 (4-C).

$[\alpha]_D^{20}$ = +24.99 (c 1.0, $CHCl_3$).

All analytical data is consistent with that previously reported.[247]

**General procedure for Brown's crotylation reaction (GP1)**

*cis/trans*-2-Butene (2.0 eq.) was added to a flame-dried flask at –78 °C under $N_2$ atmosphere followed by addition of *t*-BuOK (1.0 M in THF, 1.2 eq.) in THF (0.5 M) at –78 °C; *n*-BuLi (1.6 M, 1.2 eq.) was added and the mixture stirred for 30 min at -45 °C. Then the reaction mixture was re-cooled to –78 °C, and (+)/(–)-B-methoxydiisopinocampheylborane [(+)/(–)-$Ipc_2BOMe$] (1.8 eq.) dissolved in THF (3.4 M) was added dropwise and stirred for 1 hr at –78 °C. After that $BF_3{\cdot}OEt_2$ (2.0 eq.) was added dropwise followed by dropwise addition of aldehyde (1.0 eq.) in THF (9.3 M) to the reaction mixture at –78 °C and the mixture stirred for 3 hrs at that temperature. The reaction mixture was oxidised with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at room temperature (60 °C, when R = TBDPS). The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography on silica gel to afford the pure olefin.



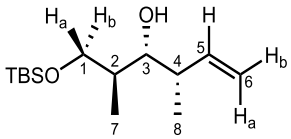

**246**, $P^1$ = TBS,

**248**, (*anti*, *syn*), 71%, dr = 9:1
**249**, (*anti*, *anti*), 64%, dr = 20:1
**277**, (*syn*, *syn*), 68%, dr = 22:1
**278**, (*syn*, *anti*), 63%, dr = 20:1

**288**, $P^1$ = TBDPS,

**289**, (*syn*, *syn*), 74%, dr = 30:1
**290**, (*anti*, *syn*), 70%, dr = 19:1
**291**, (*syn*, *anti*), 73%, dr = 19:1
**292**, (*anti*, *anti*), 66%, dr = 30:1

**(2S,3R,4S)-1-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (248)**




According to general procedure GP1, *cis*-2-butene (0.65 mL, 6.72 mmol), *t*-BuOK (4.03 mL, 4.03 mmol), *n*-BuLi (2.52 mL, 4.03 mmol), [(+)-$Ipc_2BOMe$] (1.91 g, 6.05 mmol), $BF_3{\cdot}OEt_2$ (0.64 mL, 6.72 mmol), and aldehyde **246** (680 mg, 3.36 mmol) afforded after purification by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *anti*, *syn*-olefin (621 mg, 71%) as a colourless oil.

**$R_f$**: 0.48 (ethyl acetate : petroleum ether = 1:20)

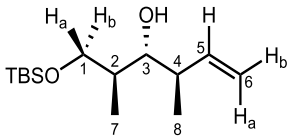
**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.86 (ddd, *J* = 17.5, 10.4, 7.3 Hz, 1H, 5-H), 5.12 – 4.96 (m, 2H, 6-$H_{a,b}$), 3.84 (dd, *J* = 11.9, 3.4 Hz, 1H, 1-$H_b$), 3.62 – 3.54 (m, 2H, 1-$H_a$+3-H), 3.40 (s, 1H, OH), 2.34 (m, 1H, 4-H), 1.82 – 1.73 (m, 1H, 2-H), 1.05 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.90 (d, *J* = 7.0 Hz, 3H, 7-$CH_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.07 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.4 (5-C), 113.8 (6-C), 79.5 (3-C), 67.9 (1-C), 41.3 (4-C), 36.6 (2-C), 25.8 (3C, C($CH_3$)$_3$), 18.1 ($C(CH_3)_3$), 14.1 (8-$CH_3$), 13.4 (7-$CH_3$), –5.6 (Si-$CH_3$), –5.7 (Si-$CH_3$).

$[\alpha]_D^{20}$ = +5.34 (c 0.9, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +6.4 (c 2.0, $CHCl_3$)].

All analytical data is consistent with that previously reported.[246]

**(2S,3R,4R)-1-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (249)**




According to general procedure GP1, *trans*-2-butene (0.65 mL, 6.72 mmol), *t*-BuOK (4.03 mL, 4.03 mmol), *n*-BuLi (2.52 mL, 4.03 mmol), [(+)-$Ipc_2BOMe$] (1.91 g, 6.05 mmol), $BF_3{\cdot}OEt_2$ (0.64 mL, 6.72 mmol), and aldehyde **246** (680 mg, 3.36 mmol)

afforded after purification by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *anti*, *anti*-olefin **249** (559 mg, 64%) as a colourless oil.

**$R_f$**: 0.35 (ethyl acetate : petroleum ether = 1:20)

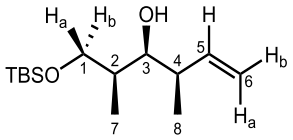
**$^1$H NMR** (400 MHz, Chloroform-d) δ 6.00 – 5.88 (m, 1H, 5-H), 5.07 – 5.03 (m, 2H, 6-$H_{a,b}$), 3.80 (dd, *J* = 2.9, 0.7 Hz, 1H, 3-H), 3.75 (dd, *J* = 10.0, 4.2 Hz, 1H, 1-$H_b$), 3.62 (dd, *J* = 10.0, 8.0 Hz, 1H, 1-$H_a$), 3.39 (s, 1H, OH), 2.39 – 2.31 (m, 1H, 4-H), 1.84 – 1.72 (m, 1H, 2-H), 1.11 (d, *J* = 6.9 Hz, 3H, 8-$CH_3$), 0.90 (s, 9H, $C(CH_3)_3$), 0.82 (d, *J* = 6.9 Hz, 3H, 7-$CH_3$), 0.08 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 140.0 (5-C), 114.9 (6-C), 80.3 (3-C), 68.7 (1-C), 41.3 (4-C), 37.6 (2-C), 25.8 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 17.7 (8-$CH_3$), 13.4 (7-$CH_3$), –5.5 (Si-$CH_3$), –5.6 (Si-$CH_3$).

$[\alpha]_D^{20}$ = +14.4 (c 1.1, $CHCl_3$).

All analytical data is consistent with that previously reported.[248]

**(*2S,3S,4R*)-1-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (277)**




According to general procedure GP1, *cis*-2-butene (0.65 mL, 6.72 mmol), *t*-BuOK (4.03 mL, 4.03 mmol), *n*-BuLi (2.52 mL, 4.03 mmol), [(–)-$Ipc_2$BOMe] (1.91 g, 6.05 mmol), $BF_3{\cdot}OEt_2$ (0.64 mL, 6.72 mmol), and aldehyde **246** (680 mg, 3.36 mmol) afforded after purification by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn*, *syn*-olefin **277** (590 mg, 68%) as a colourless oil.

**$R_f$**: 0.37 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.61 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H, 5-H), 5.04 (dd, *J* = 17.0, 1.8 Hz, 1H, 6-$H_a$), 4.95 (dd, *J* = 10.2, 1.8 Hz, 1H, 6-$H_b$), 3.77 (dd, *J* = 9.8, 3.3 Hz, 1H, 1-$H_b$), 3.66 (dd, *J* = 9.8, 4.0 Hz, 1H, 1-$H_a$), 3.56 (dd, *J* = 9.2, 1.6 Hz, 1H, 3-H), 3.19 (s, 1H, OH), 2.35 – 2.23 (m, 4-H), 1.72 – 1.81 (m, 1H, 2-H), 1.09 (d, *J* = 6.7

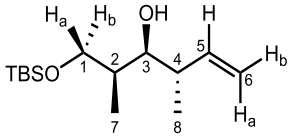
Hz, 3H, 8-$CH_3$), 0.94 (d, *J* = 7.0 Hz, 3H, 7-$CH_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 141.4 (5-C=C-), 114.5 (6-C=C-), 78.4 (3-C), 69.5 (1-C), 42.3 (4-C), 36.3 (2-C), 25.9 (3C, $C(CH_3)_3$), 18.3 ($C(CH_3)_3$), 17.3 (8-$CH_3$), 9.4 (7-$CH_3$), –5.5 (Si-$CH_3$), –5.6 (Si-$CH_3$).

$[\alpha]_D^{20}$ = +15.0 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +17.0 (c 1.0, $CHCl_3$)].

All analytical data is consistent with that previously reported.[249]

**(2S,3S,4S)-1-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (278)**




According to general procedure GP1, *trans*-2-butene (0.65 mL, 6.72 mmol), *t*-BuOK (4.03 mL, 4.03 mmol), *n*-BuLi (2.52 mL, 4.03 mmol), [(–)-$Ipc_2BOMe$] (1.91 g, 6.05 mmol), $BF_3{\cdot}OEt_2$ (0.64 mL, 6.72 mmol), and aldehyde **246** (680 mg, 3.36 mmol) afforded after purification on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn, anti*-olefin **278** (546 mg, 63%) as a colourless oil.

**$R_f$**: 0.31 (ethyl acetate : petroleum ether = 1:20)

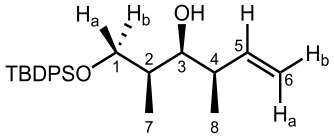
**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.82 (ddd, *J* = 17.1, 10.2, 8.3 Hz, 1H, 5-H), 5.15 – 5.03 (m, 2H, 6-$H_{a,b}$), 3.76 – 3.64 (m, 2H, 1-$H_{a,b}$), 3.52 (dd, *J* = 8.7, 2.4 Hz, 1H, 3-H), 2.75 (s, 1H, OH), 2.26 (m, 1H, 4-H), 1.85 – 1.76 (dtq, *J* = 4.7, 2.4, 7.0 Hz, 1H, 2-H), 0.94 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.93 (d, *J* = 7.0 Hz, 3H, 7-$CH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.1 (5-C), 115.1 (6-C), 76.8 (3-C), 68.4 (1-C), 41.8 (4-C), 36.2 (2-C), 25.9 (3C, $C(CH_3)_3$), 18.2 ($C(CH_3)_3$), 16.6 (8-$CH_3$), 9.3 (7-$CH_3$), –5.5 (Si-$CH_3$), –5.6 (Si-$CH_3$).

$[\alpha]_D^{20}$ = –3.6 (c 0.8, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = –0.6 (c 2.6, $CHCl_3$)].

All analytical data is consistent with that previously reported.[246]

**(*2S,3S,4R*)-1-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (289)**




According to general procedure GP1, *cis*-2-butene (2.76 mL, 28.87 mmol), *t*-BuOK (17.32 mL, 17.32 mmol), *n*- BuLi (10.83 mL, 17.32 mmol), [(–)-$Ipc_2BOMe$] (8.22 g, 26.0 mmol), $BF_3{\cdot}OEt_2$ (3.56 mL, 28.87 mmol), and aldehyde **288** (4.71 g, 14.44 mmol) afforded after purification by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn*, *syn*-olefin **289** (3.83 g, 70%) as a colourless oil.

**$R_f$**: 0.33 (ethyl acetate : petroleum ether = 1:20)

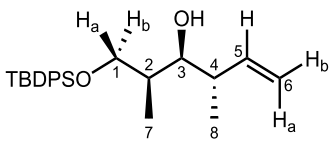
**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.71 - 7.66 (m, 4H, Ar-H), 7.46 – 7.38 (m, 6H, Ar-H), 5.62 (ddd, *J* = 16.8, 15.1, 9.9 Hz, 1H, 5-H), 5.06 (dd, *J* = 16.8, 5.2 Hz, 1H, 6-$H_a$), 4.98 (dd, *J* = 9.9, 5.2 Hz, 1H, 6-$H_b$), 3.77 (dd, *J* = 9.8, 3.5 Hz, 1H, 3-H), 3.66 (m, 2H, 1-$H_{a,b}$), 2.86 (s, 1H, OH), 2.38 – 2.25 (m, 1H, 4-H), 1.85 – 1.79 (m, 1H, 2-H), 1.12 (d, *J* = 6.6 Hz, 3H, 8-$CH_3$), 1.07 (s, 9H, $C(CH_3)_3$), 0.97 (d, *J* = 6.9 Hz, 3H, 7-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 141.2 (5-C), 135.6 (Ar-C) , 133.1 (Ar-C), 132.9 (Ar-C), 129.8 (Ar-C), 129.8 (Ar-C), 127.7 (Ar-C), 114.5 (6-C), 77.6 (3-C), 69.4 (1-C), 42.1 (4-C), 36.6 (2-C), 26.9 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$), 17.1 (8-$CH_3$), 9.5 (7-$CH_3$).

$[\alpha]_D^{20}$ = +10.5 (c 1.1, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +2.4 (c 1.0, $CHCl_3$)].

All analytical data is consistent with that previously reported.[250]

**(*2S,3S,4S*)-1-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (290)**




According to general procedure GP1, *trans*-2-butene (0.55 mL, 6.13 mmol), potassium *t*-BuOK (3.68 mL, 3.68 mmol), *n*-BuLi (2.30 mL, 3.68 mmol), [(–)-$Ipc_2BOMe$] (1.74 g, 5.51 mmol), $BF_3{\cdot}OEt_2$ (0.76mL, 6.13 mmol), and aldehyde **288** (1.0 g, 3.06 mmol) afforded after purification by chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn, anti*-olefin **290** (855 mg, 73%) as a colourless oil.

**$R_f$**: 0.26 (ethyl acetate : petroleum ether = 1:20)

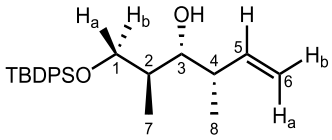
**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.70 – 7.66 (m, 4H, Ar-H), 7.46 – 7.36 (m, 6H, Ar-H), 5.83 (ddd, *J* = 17.1, 10.7, 8.4 Hz, 1H, 5-H), 5.16 – 5.05 (m, 2H, 6-$H_{a,b}$), 3.72 (d, *J* = 5.2 Hz, 2H, 1-$H_{a,b}$), 3.59 (dd, *J* = 8.5, 2.7 Hz, 1H, 3-H), 2.41 (s, 1H, OH), 2.32 – 2.21 (m, 1H, 4-H), 1.89 – 1.78 (m, 1H, 2-H), 1.07 (s, 9H, $C(CH_3)_3$), 0.96 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.95 (d, *J* = 6.4 Hz, 3H, 7-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 141.9 (5-C), 135.6 (Ar-C), 133.3 (Ar-C), 129.7 (Ar-C), 127.6 (Ar-C), 115.4 (6-C), 76.1 (3-C), 68.4 (1-C), 41.8 (4-C), 36.7 (2-C), 26.9 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$), 16.7 (8-$CH_3$), 9.6 (7-$CH_3$).

$[\alpha]_D^{20}$ = + 13.2 (c 0.9, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +4.9 (c 2.8, $CHCl_3$)].

All analytical data is consistent with that previously reported.[251]

**(*2S,3R,4S*)-1-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (291)**




According to general procedure GP1, *cis*-2-butene (0.55 mL, 6.13 mmol), *t*-BuOK (3.68 mL, 3.68 mmol), *n*-butyllithium (2.30 mL, 3.68 mmol), [(+)-$Ipc_2$BOMe] (1.74 g, 5.51 mmol), $BF_3{\cdot}OEt_2$ (0.76mL, 6.13 mmol), and aldehyde **288** (1.0 g, 3.06 mmol) afforded after purification by chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *anti*, *syn*-olefin **291** (820 mg, 70 %) as a colourless oil.

**$R_f$**: 0.38 (ethyl acetate : petroleum ether = 1:20)

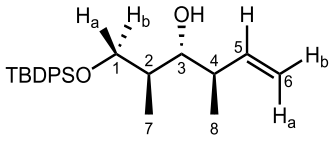
**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.70 – 7.68 (m, 4H, Ar-H), 7.48 – 7.37 (m, 6H, Ar-H), 5.93 – 5.81 (m, 1H, 5-H), 5.08 – 4.93 (m, 2H, 6-$H_{a,b}$), 3.83 (dd, *J* = 10.1, 4.0 Hz, 1H, 1-$H_b$), 3.65 (dd, *J* = 10.1, 6.2 Hz, 1H, 1-$H_a$,), 3.49 (dd, *J* = 7.0, 4.0 Hz, 1H, 3-H), 3.40 (s, 1H, OH), 2.35 (m, 1H, 2-H), 1.84 (m, 1H, 4-H), 1.08 (d, *J* = 7.0 Hz, 7-$CH_3$), 1.07 (s, 9H, $C(CH_3)_3$), 0.91 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.4 (5-C), 135.6 (Ar-C), 132.8 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 114.0 (1-C), 79.1 (3-C), 68.4 (1-C), 41.0 (4-C), 36.9 (2-C), 26.8 (3, $C(CH_3)_3$), 19.1 ($C(CH_3)_3$), 14.1 (8-$CH_3$), 13.1 (8-$CH_3$).

$[\alpha]_D^{20}$ = +1.7 (c 1.2, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +2.3 (c 2.5, $CHCl_3$)].

All analytical data is consistent with that previously reported.[252]

**(*2S,3R,4R*)-1-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (292)**




According to general procedure GP1, *trans*-2-butene (0.55 mL, 6.13 mmol), *t*-BuOK (3.68 mL + 3.55 mL THF, 3.68 mmol), *n*-BuLi (2.30 mL, 3.68 mmol), [(–)-$Ipc_2BOMe$] (1.74 g + 1.63 mL THF, 5.51 mmol), $BF_3{\cdot}OEt_2$ (0.76mL, 6.13 mmol), and aldehyde **288** (1.0 g, 3.06 mmol) afforded after purification by chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *anti, anti*-olefin **292** (773 mg, 66 %) as a colourless oil.

**$R_f$**: 0.30 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.68 (m, 4H, Ar-H), 7.47 – 7.37 (m, 6H, Ar-H), 5.94 (ddd, *J* = 17.2, 10.5, 8.4 Hz, 1H, 5-H), 5.12 – 5.02 (m, 2H, 6-$H_{a,b}$), 3.76 – 3.64 (m, 2H, 1-$H_{a,b}$), 3.52 (s, OH), 3.43 (dd, *J* = 7.3, 3.5 Hz, 1H, 3-H), 2.45 – 2.30 (m, 1H, 4-H), 1.84 (m, 1H, 2-H), 1.11 (d, *J* = 6.9 Hz, 3H, 8-$CH_3$), 1.05 (s, 9H, $C(CH_3)_3$), 0.80 (d, *J* = 7.0 Hz, 3H, 7-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 139.9 (5-C), 135.6 (Ar-C), 132.9 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 115.1 (6-C), 79.8 (3-C), 69.0 (1-C), 41.2 (4-C), 37.8 (2-C), 26.8 (3C, $C(CH_3)_3$), 19.1 ($C(CH_3)_3$), 17.8 (8-$CH_3$), 13.6 (8-$CH_3$).

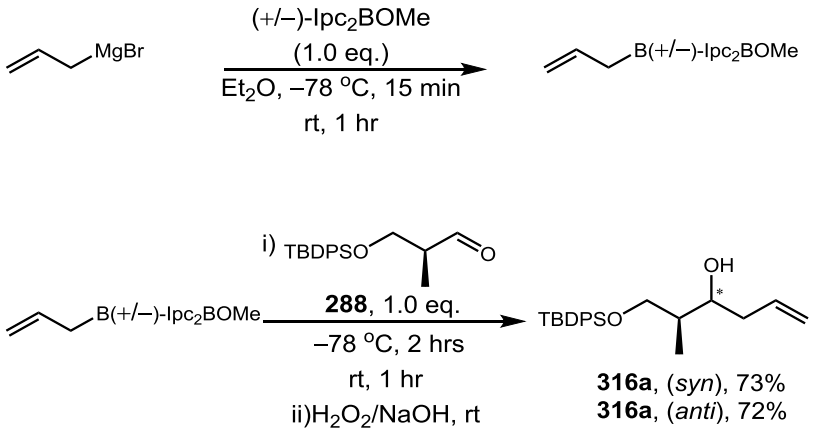
$[\alpha]_D^{20}$ = +12.7 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +16 (c 2.1, $CHCl_3$)].

All analytical data is consistent with that previously reported. [252]

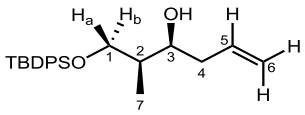
**General procedure for allylation reaction (GP2)**

To a solution of (+)/(–)-B-methoxydiisopinocampheylborane [(+)/(–)-$Ipc_2BOMe$] (1.0 eq.) dissolved in $Et_2O$ (1.0 M) was added dropwise allyl magnesium bromide (1.0 eq.,

1.0 M in THF) at –78 °C under $N_2$ atmosphere. The reaction mixture was stirred at –78 °C for 15 min and additional 1 hr at room temperature followed by addition of aldehyde **288** (1.0 eq.) at –78 °C. After stirred at –78 °C for 2 hrs and another 1 hr at room temperature, the reaction was oxidised by with 3 M NaOH and 30% $H_2O_2$ overnight at room temperature. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography on silica gel to afford the pure olefin.




**(*2S,3S*)-1-((tert-butyldiphenylsilyl)oxy)-2-methylhex-5-en-3-ol (316a)**



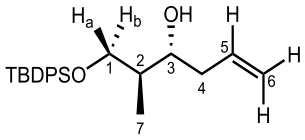

According to general procedure GP2, allyl magnesium bromide (3.06 mL, 3.06 mmol) [(–)-Ipc$_2$BOMe] (966 mg, 3.06 mmol), and aldehyde 288 (1.0 g, 3.06 mmol) afforded after purification by chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn*-olefin **316a** (823 mg, 73%) as a colourless oil.

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.70 – 7.64 (m, 4H, Ar-H), 7.46 – 7.37 (m, 6H, Ar-H), 5.89 – 5.81 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H, 5-H), 5.15 – 5.05 (m, 2H, 6-H), 3.96 – 3.92 (m, 1H, 3-H), 3.75 (dd, *J* = 10.1, 4.3 Hz, 1H, 1-H$_b$), 3.68 (dd, *J* = 10.1, 5.7 Hz, 1H, 1-H$_a$), 2.76 (brs, 1H, OH), 2.33 – 2.26 (m, 1H, 4-H), 2.24 – 2.14 (m, 1H, 4-H), 1.84 – 1.73 (m, 1H, 2-H), 1.06 (s, 9H, C(CH$_3$)$_3$), 0.95 (d, *J* = 7.0 Hz, 3H, 7-CH$_3$).

$[\alpha]_D^{20}$ = +7.0 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = –6.3 (c 3.4, $CH_2Cl_2$), for ***ent*-(2*R*,3*R*)-316a**].

All analytical data is consistent with that previously reported.[253]

**(2*S*,3*R*)-1-((tert-butyldiphenylsilyl)oxy)-2-methylhex-5-en-3-ol (316b)**



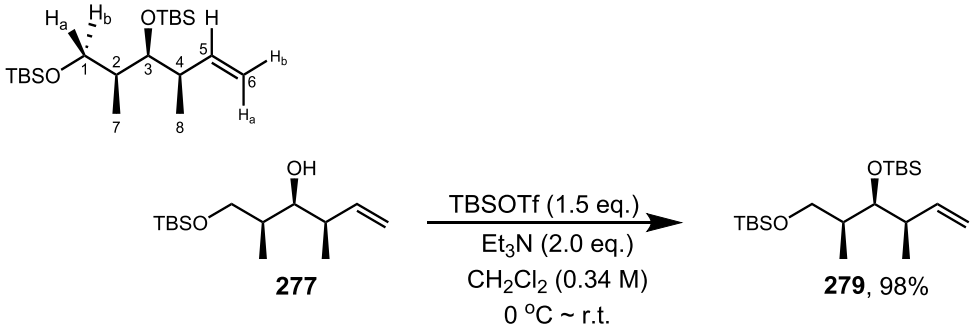

According to general procedure GP2, allyl magnesium bromide (3.06 mL, 3.06 mmol) [(+)-$Ipc_2BOMe$] (966 mg, 3.06 mmol), and aldehyde 288 (1.0 g, 3.06 mmol) afforded after purification by chromatography on silica gel (ethyl acetate : petroleum ether = 1:70 ~ 1:50) *syn*-olefin **316a** (812 mg, 72%) as a colourless oil.

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.72 – 7.65 (m, 4H, Ar-H), 7.48 – 7.37 (m, 6H, Ar-H), 6.00 – 5.88 (m, 1H, 5-H), 5.17 – 5.10 (m, 2H, 6-H), 3.77 (dd, *J* = 10.2, 4.4 Hz, 1H, 1-$H_b$), 3.72 – 3.68 (m, 1H, 3-H), 3.65 (dd, *J* = 10.2, 5.1 Hz, 1H, 1-$H_a$), 3.46 (brs, 1H, OH), 2.43 – 2.32 (m, 1H, 4-H), 2.27 – 2.15 (m, 1H, 4-H), 1.17 (m, 1H, 2-H), 1.06 (s, 9H, $C(CH_3)_3$), 0.86 (d, *J* = 7.0 Hz, 1H, 7-$CH_3$).

$[\alpha]_D^{20}$ = +16 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = –17 (c 2.4, $CH_2Cl_2$), for ***ent*-(2*R*,3*S*)-316b**].

All analytical data is consistent with that previously reported.[253]

**(5*S*,6*S*)-5-((*R*)-but-3-en-2-yl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (279)**



To a solution of alcohol **277** (300 mg, 1.16 mmol) in $CH_2Cl_2$ (3.4 mL) at 0 °C were added successively triethylamine (0.32 mL, 2.32 mmol) and TBSOTf (0.40 mL, 1.74 mmol). The reaction mixture was stirred for 30 min at 0 °C, then allowed to slowly warm to room temperature and stirred for 5 hrs. A saturated aqueous solution of $NaHCO_3$ was added, the two phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to afford compound **279** (425.6 mg, 98 %) as a colourless oil.

**$R_f$**: 0.86 (ethyl acetate : petroleum ether = 1:20)

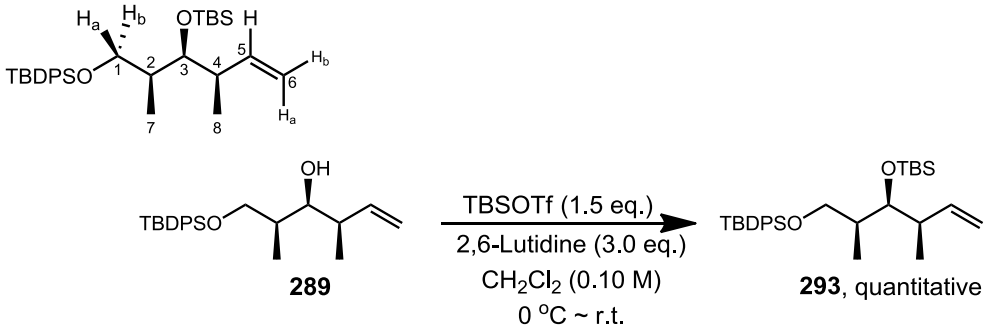
**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.80 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H, 5-H), 5.07 – 4.88 (m, 2H, 6-$H_{a,b}$), 3.67 (dd, *J* = 6.9, 2.3 Hz, 1H, 3-H), 3.43 (dd, *J* = 9.9, 7.9 Hz, 1H, 1-$H_a$), 3.35 (dd, *J* = 9.9, 6.6 Hz, 1H, 1-$H_b$), 2.42 – 2.25 (m, 1H, 4-H), 1.84 – 1.69 (m, 1H, 2-H), 0.99 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.90 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.79 (d, *J* = 6.8 Hz, 3H, 7-$CH_3$), 0.05 (s, 2 × Si-$CH_3$, 6H), 0.02 (s, 6H, 2 × Si-$CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.2 (5-C), 113.3 (6-C), 74.9 (3-C), 65.9 (1-C), 42.7 (4-C), 38.8 (2-C), 26.1 (3C, $C(CH_3)_3$), 25.9 (3C, $C(CH_3)_3$), 18.4 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), 16.9 (8-$CH_3$), 10.6 (7-$CH_3$), –3.8 (Si-$CH_3$), –4.2 (Si-$CH_3$), –5.3 (Si-$CH_3$), –5.4 (Si-$CH_3$).

$[\alpha]_D^{20}$ = +19.2 (c 1.0, $CHCl_3$) [lit: $[\alpha]_D^{20}$ = +21.2 (c 1.0, $CHCl_3$)].

All analytical data is consistent with that previously reported.[254]

**(5S,6S)-5-((R)-but-3-en-2-yl)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (293)**



To a solution of alcohol **289** (769 mg, 2.01 mmol) in $CH_2Cl_2$ (20.0 mL) at 0 ºC were added successively 2,6-lutidine (0.70 mL, 6.03 mmol) and TBSOTf (0.69 mL, 3.01 mmol). The reaction mixture was allowed to slowly warm to rt and stirred for 5 hrs. A saturated aqueous solution of $NaHCO_3$ was added, the two phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:50 ~ 1:20) to afford compound **293** (998.7 mg, 100%) as colourless oil.

**$R_f$**: 0.95 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.65 (m, 4H, Ar-H), 7.38 (m, 6H, Ar-H), 5.80 (ddd, *J* = 17.7, 10.4, 7.6 Hz, 1H, 5-H), 5.03 – 4.92 (m, 2H, 6-$H_{a,b}$), 3.76 (dd, *J* = 6.7, 2.2 Hz, 1H, 3-H), 3.53 (dd, *J* = 10.0, 7.9 Hz, 1H, 1-$H_a$), 3.40 (dd, *J* = 10.0, 6.5 Hz, 1H, 1-$H_b$), 2.34 (m, 1H, 4-H), 1.83 (m, 1H, 2-H), 1.06 (s, 9H, $C(CH_3)_3$), 0.99 (d, *J* = 6.8 Hz, 3H, 8-$CH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.77 (d, *J* = 6.8 Hz, 3H, 7-$CH_3$), 0.02 (s, 6H, 2 × Si-$CH_3$).

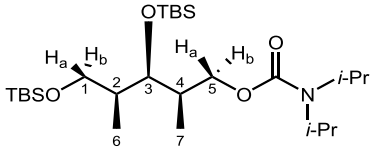
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 142.2 (5-C), 135.6 (Ar-C), 134.0 (Ar-C), 129.5 (Ar-C), 127.5 (Ar-C), 113.4 (6-C), 74.9 (3-C), 66.9 (1-C), 42.8 (4-C), 38.6 (2-C), 26.9 (3C, C(*C*$H_3$)$_3$), 26.1 (3C, C(*C*$H_3$)$_3$), 19.2 (*C*($CH_3$)$_3$), 18.4 (*C*($CH_3$)$_3$), 16.7 (8-$CH_3$), 10.7 (7-$CH_3$), –3.7 (Si-$CH_3$), –4.1 (Si-$CH_3$).

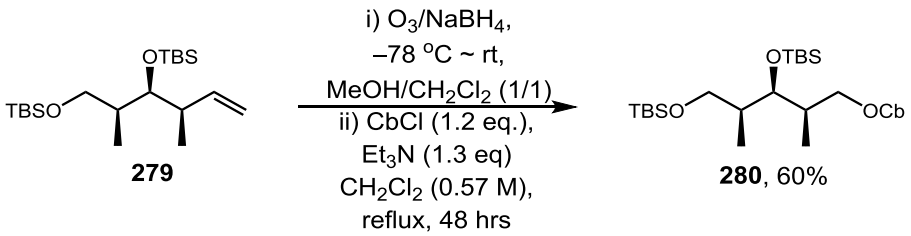
**HRMS** (ESI) calc'd for $C_{30}H_{48}O_2Si_2Na$ $[M+Na]^+$: 519.3085; found: 519.3082.

$[\alpha]_D^{20}$ = +6.0 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ :3072, 2957, 2856, 1428, 1462, 1253, 1107, 876, 835, 773, 739, 700, 613.

**(*2R,3S,4S*)-3,5-bis((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentyl diisopropylcarbamate (280)**






To a solution of compound **279** (500 mg, 1.3 mmol) in MeOH (3.4 mL) and $CH_2Cl_2$ (3.4 mL) was added some drops of Sudan-III solution indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition of $NaBH_4$ (507.5 mg, 13.4 mmol). The reaction was stirred for 1 hr at –78 °C, then it was allowed to warm up to rt and stirred overnight. After that water was added, and the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude oil was subjected to next step without further purification.

A solution of crude alcohol from last step, diisopropyl carbamoyl chloride (CbCl) (264.4 mg, 1.6 mmol) and $Et_3N$ (0.24 mL, 1.7 mmol) in anhydrous $CH_2Cl_2$ (2.4 mL) was heated under reflux for 48 hrs. Then, the reaction mixture was poured in water and extracted with diethyl ether (×3). The combined organic phases were washed with water, brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:50 ~ 1:20) to afford pure carbamate **280** (405.6 mg, 60%).

**R**$_f$: 0.44 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 4.03 (dd, *J* = 10.5, 6.0 Hz, 1H, 5-$H_b$), 3.93 (dd, *J* = 10.5, 7.4 Hz, 1H, 5-$H_a$), 3.77 (t, *J* = 4.0 Hz, 3H, 3-H), 3.50 (dd, *J* = 9.7, 6.6 Hz, 1H, 1-H), 3.37 (dd, *J* = 9.7, 6.7 Hz, 1H, 1-H), 2.03 (m, 1H, 4-H), 1.78 (m, 1H, 2-H), 1.21 (d, *J* = 6.9 Hz, 12H, 2 × CH(C*H*$_3$)$_2$), 0.94 (d, *J* = 6.9 Hz, 3H, 7-$CH_3$), 0.90 (s, 9H, C($CH_3$)$_3$), 0.88 (s, 9H, C($CH_3$)$_3$), 0.86 (d, *J* = 7.0 Hz, 3H, 6-$CH_3$), 0.05 (s, 3H, Si-$CH_3$), 0.05 (s, 3H, Si-$CH_3$), 0.02 (s, 6H, 2 × Si-$CH_3$)

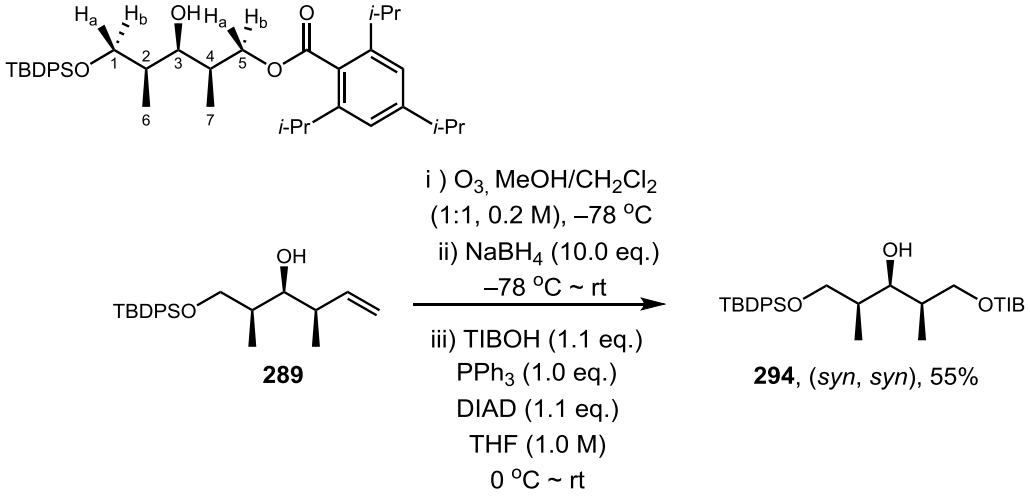
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 155.7 (C=O), 72.9 (3-C), 67.6 (5-C), 65.8 (1-C), 39.6 (2-C), 37.5 (4-C), 26.1 (3C, C($CH_3$)$_3$), 25.9 (3C, C($CH_3$)$_3$), 18.4 ($C$($CH_3$)$_3$), 18.3 ($C$($CH_3$)$_3$), 13.2 (7-$CH_3$), 12.3 (6-$CH_3$), –4.0 (Si-$CH_3$), –4.1 (Si-$CH_3$), –5.3 (Si-$CH_3$), –5.4 (Si-$CH_3$).

**HRMS** (ESI) calc'd for $C_{26}H_{57}O_4Si_2NaN$ $[M+Na]^+$: 526.3724; found: 526.3729.

$[\alpha]_D^{20}$ = +18.7 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 2957, 2930, 2857, 1695, 1463, 1472, 1367, 1290, 1252, 1092, 1047, 834, 771, 672.

**(*2R,3S,4S*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,4-dimethylpentyl 2,4,6 triisopropylbenzoate (294)**




To a solution of olefin **294** (3.83 g, 10.0 mmol) in MeOH (25 mL) and $CH_2Cl_2$ (25 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (3.78 g, 100.0 mmol). The reaction was stirred for 1 hr at –78 °C, then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (2.73 g, 11.0 mmol) and $PPh_3$ (2.62 g, 10.0 mmol) and THF (2.5 mL, 1.0 M) under $N_2$. The reaction mixture was cooled to 0 °C, and DIAD (2.2 mL, 2.22 g, 11.0 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuo. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:30) to afford benzoate ester **294** as a colourless oil (3.38 g, 55 %).

**$R_f$**: 0.23 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.64 (ddd, *J* = 8.0, 4.2, 1.6 Hz, 4H, Ar-H), 7.46 – 7.33 (m, 6H, Ar-H), 6.99 (s, 2H, Ar-H), 4.34 (dd, *J* = 11.0, 5.2 Hz, 1H, 5-$H_b$), 4.11 (dd, *J* = 11.0, 6.1 Hz, 1H, 5-$H_a$), 3.75 (dd, *J* = 4.0, 2.6 Hz, 1H, 3-H), 3.70 (dd, *J* = 10.1, 4.2 Hz, 1H, 1-$H_b$), 3.64 (dd, *J* = 10.1, 4.7 Hz, 1H, 1-$H_a$), 2.84 (hept, *J* = 7.0 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.69 (s, 1H, OH), 2.10 – 2.05 (m, 1H, 4-H), 1.90 – 1.78 (m, 1H, 2-H), 1.22 (d, *J* = 7.0 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.08 (d, *J* = 6.8 Hz, 3H, 7-$CH_3$), 1.04 (d, *J* = 5.7 Hz, 3H, 6-$CH_3$), 1.03 (s, 9H, C($CH_3$)$_3$).

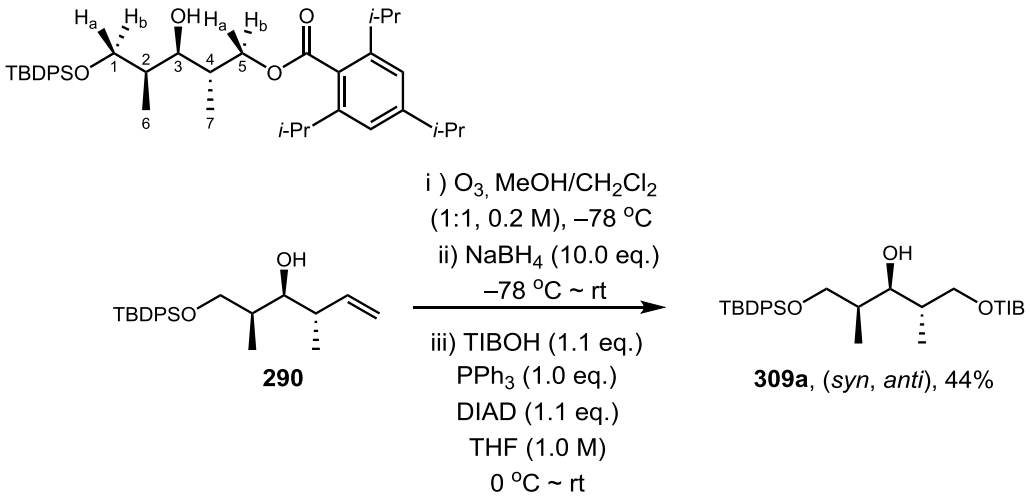
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.7 (Ar-C), 135.6 (Ar-C), 133.0 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 120.8 (Ar-C), 75.0 (3-C), 68.6 (1-C), 67.5 (5-C), 37.2 (2-C), 35.7 (4-C), 34.3 (*C*H($CH_3$)$_2$), 31.6 (2 × *C*H($CH_3$)$_2$), 26.8 (C(*C*$H_3$)$_3$), 24.2 (2 × CH(*C*$H_3$)$_2$), 23.9 (CH(*C*$H_3$)$_2$), 19.1 (*C*(*C*$H_3$)$_3$), 12.9 (7-C), 11.13 (6-C).

**HRMS** (ESI) calc'd for $C_{39}H_{56}O_4SiNa$ $[M+Na]^+$: 639.3840; found: 639.3837.

$[\alpha]_D^{20}$ = +18.8 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 3516, 2960, 1724, 1590, 1428, 1462, 1105, 1074, 877, 823, 739, 701, 614, 503.

**(*2R,3S,4R*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,4-dimethylpentyl 2,4,6 triisopropylbenzoate (309a)**




To a solution of olefin **290** (537 mg, 1.40 mmol) in MeOH (3.5 mL) and $CH_2Cl_2$ (3.5 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (531 mg, 14.0 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (384 mg, 1.54 mmol) and $PPh_3$ (368.1 mg, 1.40 mmol) and THF (1.4 mL) under $N_2$. The reaction mixture was cooled to 0 °C, and DIAD (0.30 mL, 1.54 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate : petroleum ether = 1:30) silica gel to afford benzoate ester **309a** as a colourless oil (379 mg, 44%).

**R**$_f$: 0.33 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.73 – 7.64 (m, 4H), 7.49 – 7.36 (m, 6H), 7.03 (s, 2H), 4.53 (dd, *J* = 10.8, 3.4 Hz, 1H, 5-H$_b$), 4.42 (dd, *J* = 10.8, 6.4 Hz, 1H, 5-H$_a$), 3.93 – 3.76 (dd, 2H, 1-H + 3-H), 3.72 (dd, *J* = 10.0, 4.9 Hz, 1H, 1-H), 3.06 (brs, 1H, OH), 2.92 (hept, *J* = 6.8 Hz, 3H, 3 × C*H*(CH$_3$)$_2$), 2.13 – 1.93 (m, 1H, CH), 1.91 – 1.75 (m, 1H, CH), 1.27 (d, *J* = 6.8 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.08 (s, 9H, C(CH$_3$)$_3$), 1.00 (d, *J* = 7.0 Hz, 3H, CH$_3$), 0.94 (d, *J* = 4.2 Hz, 3H, CH$_3$).

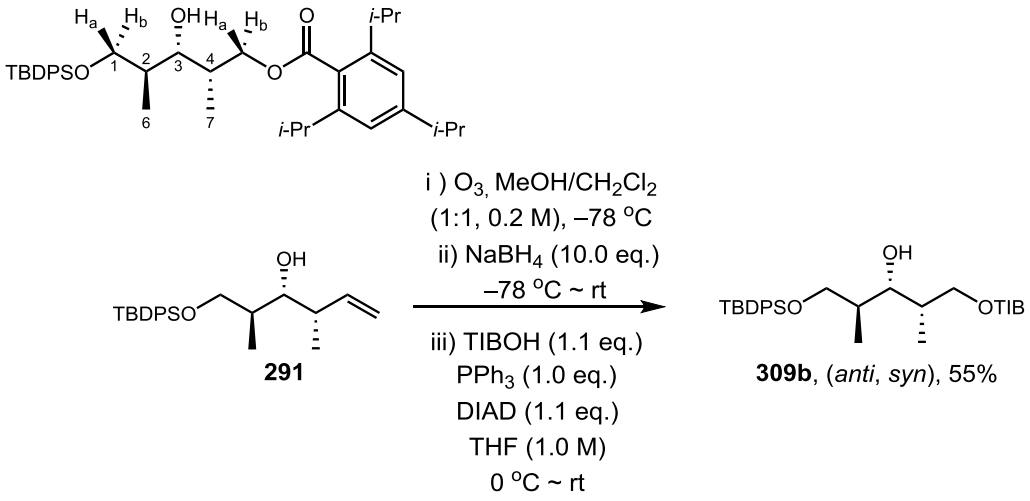
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 150.0 (Ar-C), 144.8 (Ar-C), 135.5 (Ar-C), 132.6 (Ar-C), 130.8 (Ar-C), 129.9 (Ar-C), 127.8 (Ar-C), 120.8 (Ar-C), 74.9 (3-C), 69.5 (1-C), 67.9 (5-C), 36.0 (2-C), 35.9 (4-C), 34.5 (*C*H(CH$_3$)$_2$), 31.6 (2C, 2 × *C*H(CH$_3$)$_2$), 26.9 (3C, C(*C*H$_3$)$_3$), 24.3 (4C, 2 × CH(*C*H$_3$)$_2$), 24.0 (2C, CH(*C*H$_3$)$_2$), 19.2 (*C*(CH$_3$)$_3$), 14.0 (7-C), 9.0 (6-C).

**HRMS** (ESI) calc'd for $C_{39}H_{56}O_4SiNa$ $[M+Na]^+$: 639.3840; found: 639.3839.

$[\alpha]_D^{20}$ = +7.8 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$ : 3513, 2961, 1724, 1606, 1462, 1428, 1105, 1077, 877, 823, 740.

**(*2R,3R,4R*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,4-dimethylpentyl 2,4,6 triisopropylbenzoate (309b)**




To a solution of olefin **291** (404 mg, 1.01 mmol) in MeOH (2.6 mL) and $CH_2Cl_2$ (2.6 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (399 mg, 10.5 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was

allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (288 mg, 1.16 mmol) and $PPh_3$ (276 mg, 1.06 mmol) and THF (1.1 mL) under $N_2$. The reaction mixture was cooled to 0 °C, and DIAD (0.23 mL, 1.16 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate : petroleum ether = 1:30) silica gel to afford benzoate ester **309b** (359 mg, 55%).

**R$_f$**: 0.41 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.71 – 7.63 (m, 4H, Ar-H), 7.47 – 7.36 (m, 6H, Ar-CH), 7.01 (s, 2H, Ar-H), 4.39 (dd, *J* = 10.7, 7.9 Hz, 1H, 5-$H_a$), 4.30 (dd, *J* = 10.7, 6.4 Hz, 1H, 5-$H_b$), 3.76 – 3.69 (m, 2H, 3-H + 1-H), 3.65 (dd, *J* = 10.2, 8.4 Hz, 1-H) 2.89 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.12 – 2.03 (m, 1H, CH), 1.97 – 1.84 (m, 1H, CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.05 (s, 9H, C$(CH_3)_3$), 1.00 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.70 (d, *J* = 6.9 Hz, 3H, $CH_3$).

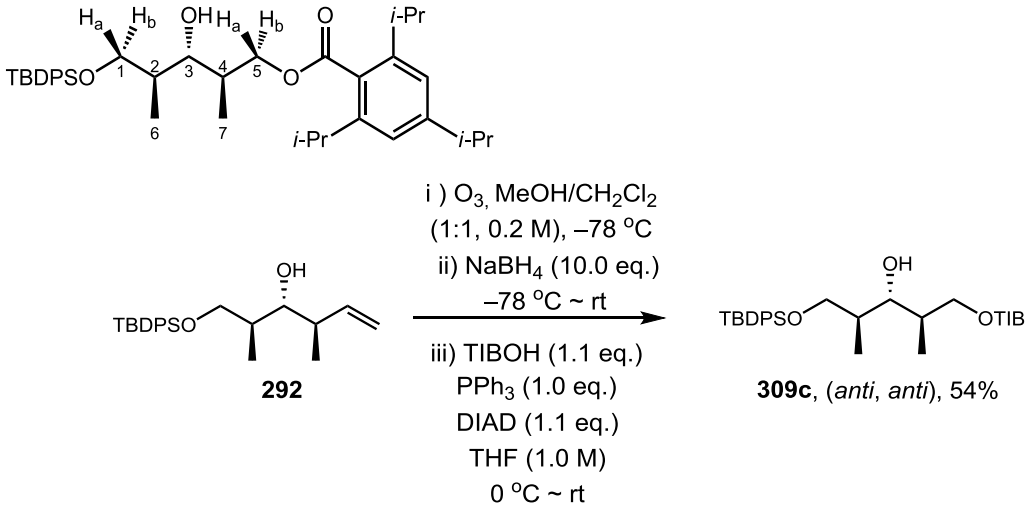
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.9 (Ar-C), 135.7 (Ar-CH), 132.8 (Ar-C), 130.9 (Ar-C), 130.1 (Ar-C), 128.0 (Ar-CH), 121.0 (Ar-CH), 75.8 (3-C), 70.3 (1-C), 67.9 (5-C), 37.4 (2-C), 35.1 (4-C), 34.6 (*C*H$(CH_3)_2$), 31.6 (2C, 2×*C*H$(CH_3)_2$), 26.9 (3C, C(*C*$H_3)_3$), 24.4 (4C, 2×CH(*C*$H_3)_2$), 24.1 (2C, CH(*C*$H_3)_2$), 19.2 (*C*$(CH_3)_3$), 13.0 (7-C), 9.5 (6-C).

**HRMS** (ESI) calc'd for $C_{39}H_{56}O_4SiNa$ $[M+Na]^+$: 639.3840; found: 639.3837.

$[\alpha]_D^{20}$ = +16.2 (c 0.9, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$ : 3503, 2961, 1724, 1606, 1463, 1428, 1105, 1070, 877, 822, 740.

**(*2R,3R,4S*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,4-dimethylpentyl 2,4,6 triisopropylbenzoate (309c)**




To a solution of olefin **292** (472 mg, 1.18 mmol) in MeOH (3.0 mL) and $CH_2Cl_2$ (3.0 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (464 mg, 12.3 mmol). The reaction was stirred for 1 hr at -78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (322 mg, 1.29 mmol) and $PPh_3$ (309 mg, 1.18 mmol) and THF (1.2 mL) under $N_2$. The reaction mixture was cooled to 0 °C, and DIAD (0.23 mL, 1.16 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash

chromatography (ethyl acetate : petroleum ether = 1:30) silica gel to afford benzoate ester **309c** (394 mg, 54%).

**$R_f$**: 0.37 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.74 – 7.63 (m, 4H, Ar-CH), 7.48 – 7.37 (m, 6H, Ar-CH), 7.02 (s, 2H, Ar-CH), 4.60 (dd, *J* = 10.9, 3.8 Hz, 1H, 5-$H_b$), 4.32 (dd, *J* = 10.9, 8.1 Hz, 1H, 5-$H_a$), 3.82 (dd, *J* = 10.3, 3.9 Hz, 1H, 1-$H_b$), 3.76 (s, 1H, OH), 3.66 (dd, *J* = 10.3, 6.8 Hz, 1H, 1-$H_a$), 3.53 (dd, *J* = 6.0, 8.8 Hz, 1H, 3-H), 2.90 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$)), 2.17 – 2.06 (m, 1H, CH), 2.04 – 1.92 (m, 1H, CH), 1.26 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.09 (d, *J* = 5.6 Hz, 3H, $CH_3$), 1.08 (s, 9H, C($CH_3$)$_3$), 0.95 (d, *J* = 7.0 Hz, 3H, $CH_3$).

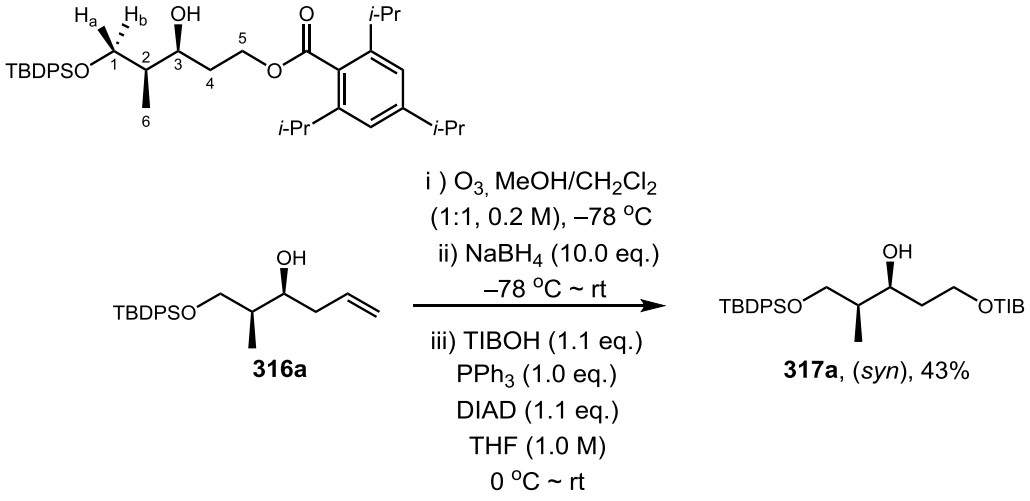
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 150.0 (Ar-C), 144.7 (Ar-C), 135.6 (Ar-C), 132.6 (Ar-C), 130.8 (Ar-C), 129.9 (Ar-C), 127.9 (Ar-C), 120.8 (Ar-C), 79.0 (3-C), 68.6 (1-C), 67.0 (5-C), 36.7 (2-C), 36.0 (4-C), 34.4 (*C*H($CH_3$)$_2$), 31.5 (2 × *C*H($CH_3$)$_2$), 26.8 (3C, C(*C*$H_3$)$_3$), 24.2 (2 × CH(*C*$H_3$)$_2$), 24.0 (CH(*C*$H_3$)$_2$), 19.0 (*C*(*C*$H_3$)$_3$), 15.2 (7-C), 14.3 (6-C).

**HRMS** (ESI) calc'd for $C_{39}H_{56}O_4SiNa$ $[M+Na]^+$: 639.3840; found: 639.3841.

$[\alpha]_D^{20}$ = +17.3 (c 1.2, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 3498, 2960, 1723, 1606, 1462, 1428, 1105, 1070, 876, 822, 740.

**(*3S,4S*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-4-methylpentyl 2,4,6-triisopropylbenzoate (317a)**



To a solution of olefin **316a** (559 mg, 1.52 mmol) in MeOH (3.8 mL) and $CH_2Cl_2$ (3.8 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (575 mg, 15.2 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (413 mg, 1.67 mmol) and $PPh_3$ (397 mg, 1.52 mmol) and THF (1.52 mL) under $N_2$ atmosphere. The reaction mixture was cooled to 0 °C, and DIAD (0.33 mL, 1.67 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash chromatography silica gel (ethyl acetate : petroleum ether = 1:30) to afford benzoate **317a** (394 mg, 43%).

**$R_f$**: 0.33 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.69 – 7.63 (m, 4H, Ar-CH), 7.46 – 7.37 (m, 6H, Ar-CH), 7.01 (s, 2H, Ar-CH), 4.49 (dd, *J* = 7.6, 5.5 Hz, 2H, 5-H), 4.04 (dd, *J* = 9.8, 3.1 Hz, 1H, 3-H), 3.77 (dd, *J* = 10.2, 4.2 Hz, 1H, 1-$H_b$), 3.67 (dd, *J* = 10.2, 5.9 Hz, 1H, 1-$H_a$), 3.04 (brs, 1H, OH), 2.88 (hept, *J* = 7.0 Hz, 3H, 3 × C*H*$(CH_3)_2$), 1.96 – 1.89 (m, 1H, 4-H), 1.87 – 1.74 (m, 2H, 4-H + 2-H), 1.24 (d, *J* = 7.0 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.05 (s, 9H, $C(CH_3)_3$), 0.94 (d, *J* = 7.1 Hz, 1H, 6-$CH_3$).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.1 (C=O), 150.2 (Ar-C), 144.9 (Ar-CH), 135.8 (Ar-CH), 135.7 (Ar-CH), 133.0 (Ar-C), 132.9 (Ar-C), 130.7 (Ar-C), 130.0 (Ar-C), 128.0 (Ar-C), 121.0 (Ar-CH), 71.4 (3-C), 68.8 (1-C), 62.7 (5-C), 39.5 (2-C), 34.6

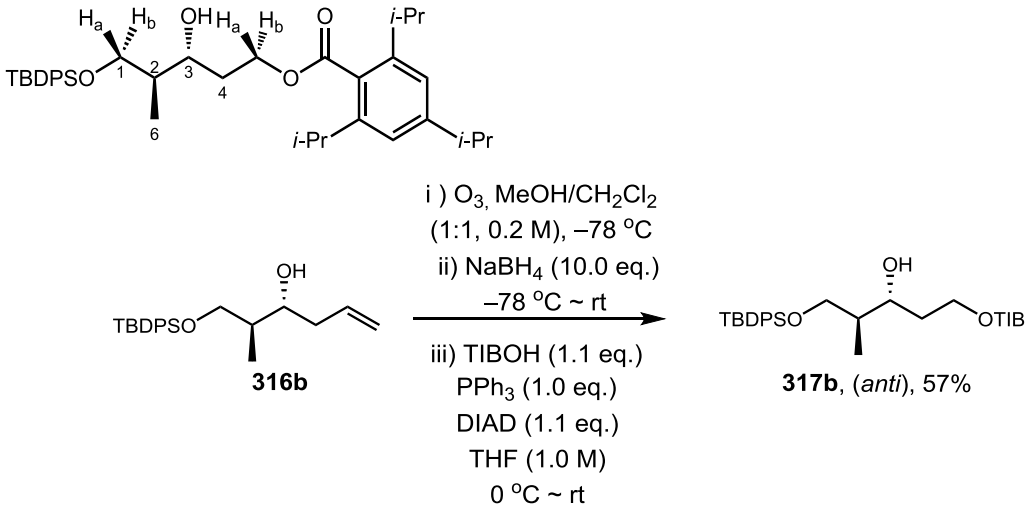
(*C*H(CH$_3$)$_2$), 33.4 (4-C), 31.6 (2 × *C*H(CH$_3$)$_2$), 27.0 (3C, C(*C*H$_3$)$_3$), 24.3 (2 × CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 19.3 (*C*(*C*H$_3$)$_3$), 10.7 (6-C).

**HRMS** (ESI) calc'd for $C_{38}H_{54}O_4SiNa$ $[M+Na]^+$: 625.3689; found: 625.3687.

$[\alpha]_D^{20}$ = –9.6 (c 0.83, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$ : 3515, 2960, 2930, 1724, 1606, 1461, 1428, 1251, 1105, 1075, 876, 823, 736, 701.

**(*3R,4S*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-4-methylpentyl 2,4,6-triisopropylbenzoate (317b)**




To a solution of olefin **316b** (1.32 g, 3.57 mmol) in MeOH (8.9 mL) and $CH_2Cl_2$ (8.9 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (1.35 g, 35.7 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was subjected to next step without further purification.

To a flame-dried tube were added crude product from last step, TIBOH (975 mg, 3.93 mmol) and $PPh_3$ (936 mg, 3.57 mmol) and THF (3.6 mL) under $N_2$. The reaction mixture was cooled to 0 °C, and DIAD (0.77 mL, 3.93 mmol) was added dropwise. The

reaction was stirred for 30 min at 0 °C, then allowed to warm up to rt and stirred for 20 hrs. After that, the reaction was quenched with sat. $NaHCO_3$ solution and water, extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resultant solid was dissolved with minimum hot dichloromethane. Then the solution was poured in ice-cold pentane. The mixture was filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate : petroleum ether = 1:30) silica gel to afford benzoate ester **317b** (1.23 g, 57%).

**$R_f$**: 0.48 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.70 – 7.66 (m, 4H, Ar-CH), 7.48 – 7.38 (m, 6H, Ar-CH), 7.02 (s, 2H, Ar-CH), 4.54 (dd, *J* = 7.8, 5.8 Hz, 2H, 5-H), 3.82 (brs, 1H, OH), 3.79 (dd, *J* = 10.0 4.2 Hz, 1H, 3-H), 3.77 (dd, *J* = 10.4, 4.1 Hz, 1H, 1-H), 3.63 (dd, *J* = 10.4, 7.6 Hz, 1H, 1-H), 2.89 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.04 – 1.98 (m, 1H, 4-H), 1.87 – 1.76 (m, 2H, 4-H + 2-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.06 (s, 9H, $C(CH_3)_3$), 0.84 (d, *J* = 7.0 Hz, 1H, 6-$CH_3$).

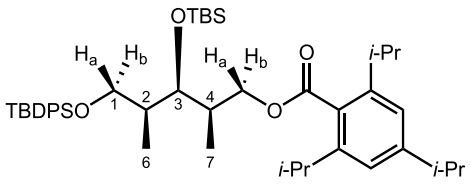
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.1 (C=O), 150.2 (Ar-C), 144.9 (Ar-CH), 135.70 (Ar-CH), 132.8 (Ar-C), 130.8 (Ar-C), 130.1 (Ar-C), 128.0 (Ar-CH), 121.0 (Ar-CH), 73.4 (3-C), 69.2 (1-C), 62.3 (5-C), 40.2 (2-C), 34.6 (*C*H$(CH_3)_2$), 34.2 (4-C), 31.6 (2C, 2 × *C*H$(CH_3)_2$), 26.9 (3C, C(*C*H$_3)_3$), 24.3 (4C, 2 × CH(*C*H$_3)_2$), 24.1 (2C, CH(*C*H$_3)_2$), 19.2 (*C*(*C*H$_3)_3$), 13.6 (6-C).

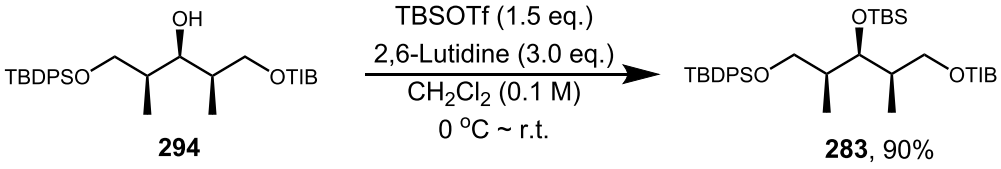
**HRMS** (ESI) calc'd for $C_{38}H_{54}O_4SiNa$ $[M+Na]^+$: 625.3689; found: 625.3691.

$[\alpha]_D^{20}$ = +21.1 (c 0.57, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 3503, 2959, 1724, 1452, 1428, 1251, 1105, 1074, 876, 822, 740, 700, 614.

**(*2R,3S,4S*)-3-((tert-butyldimethylsilyl)oxy)-5-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylpentyl 2,4,6-triisopropylbenzoate (283)**






To a solution of alcohol **294** (838 mg, 1.36 mmol) in $CH_2Cl_2$ (13.6 mL) at 0 °C were added successively 2,6-lutidine (0.48 mL, 4.07 mmol) and TBSOTf (0.47 mL, 2.04 mmol). The reaction mixture was allowed to slowly warm to rt and stirred for 5 hrs. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added, the two phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 ×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:30) to afford compound **383** (892.6 mg, 90%) as a colourless oil.

**$R_f$**: 0.83 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.67 – 7.62 (m, 4H, Ar-H), 7.44 – 7.33 (m, 6H, Ar-H), 7.00 (s, 2H, Ar-H, TIB), 4.37 (dd, *J* = 10.6, 4.8 Hz, 1H, 5-$H_b$), 4.11 (dd, *J* = 10.6, 8.7 Hz, 1H, 5-$H_a$), 3.89 (dd, *J* = 4.2, 3.1 Hz, 1H, 3-H), 3.54 (dd, *J* = 9.9, 7.2 Hz, 1H, 1-$H_a$), 3.41 (dd, *J* = 9.9, 6.7 Hz, 1H, 1-$H_b$), 2.87 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.08 (m, 1H, 4-H), 1.86 (m, 2-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.04 (s, 9H, C($CH_3$)$_3$), 0.95 (d, *J* = 6.9 Hz, 3H, 7-$CH_3$), 0.88 (s, 9H, C($CH_3$)$_3$), 0.86 (d, *J* = 6.8 Hz, 3H, 6-$CH_3$), 0.05 (s, 3H, Si-$CH_3$), –0.02 (s, 3H, Si-$CH_3$).

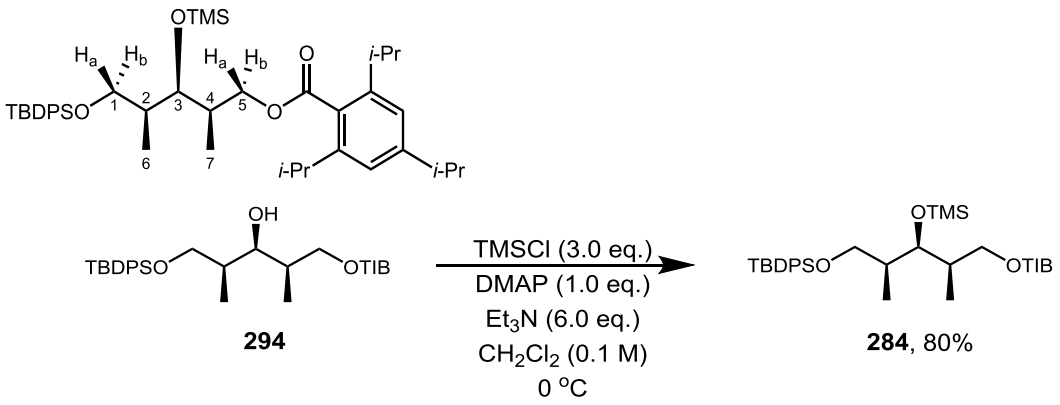
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.9 (Ar-C), 135.9 (Ar-C), 133.9 (Ar-C), 130.8 (Ar-C), 129.7 (Ar-C), 127.7 (Ar-C), 120.9 (Ar-C), 72.9 (3-C), 68.0 (5-C), 66.9 (1-C), 38.7 (2-C), 38.4 (4-C), 34.5 (*C*H($CH_3$)$_2$), 31.6 (2C, 2 × *C*H($CH_3$)$_2$), 27.0 (3C, C(*C*$H_3$)$_3$), 26.1 (3C, C(*C*$H_3$)$_3$), 24.4 (CH(*C*$H_3$)$_2$), 24.3 (CH(*C*$H_3$)$_2$), 24.1 (CH(*C*$H_3$)$_2$), 19.3 (*C*($CH_3$)$_3$), 18.4 (*C*($CH_3$)$_3$), 13.8 (7-C), 12.2 (6-C), –4.0 (Si-$CH_3$), –4.2 (Si-$CH_3$).

**HRMS** (ESI) calc'd for $C_{45}H_{70}O_4Si_2Na$ $[M+Na]^+$: 753.4705; found: 753.4702.

$[\alpha]_D^{20}$ = +19.0 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 2959, 1726, 1590, 1428, 1462, 1250, 1105, 1071, 876, 824, 773, 739, 701, 613, 504.

**(2R,3S,4S)-5-((tert-butyldiphenylsilyl)oxy)-2,4-dimethyl-3-((trimethylsilyl)oxy)pentyl 2,4,6-triisopropylbenzoate (284)**




Benzoate ester **294** (217 mg, 0.36 mmol) was dissolved in $CH_2Cl_2$ (3.6 mL) and cooled to 0 °C. DMAP (44.1 mg, 0.36 mmol), triethylamine (0.30 mL, 2.17 mmol) and TMSCl (0.14 mL, 1.08 mmol) were added sequentially. After 1.5 hrs, the reaction was quenched with aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (×3). The combined extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration under vacuo, followed by chromatography on silica gel (diethyl ethyl : pentane = 1:50) afforded benzoate ester **284** (199.1 mg, 80 %) as a colourless oil.

**$R_f$**: 0.27 (diethyl ethyl : pentane = 1:50)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.63 (m, 4H, Ar-H), 7.45 – 7.32 (m, 6H, Ar-H), 6.99 (s, 2H, Ar-H, TIB), 4.25 (dd, *J* = 10.7, 5.4 Hz, 1H, 5-$H_b$), 4.08 (dd, *J* = 10.7, 7.8 Hz, 1H, 5-$H_a$), 3.76 (t, *J* = 4.7 Hz, 1H, 3-H), 3.53 (dd, *J* = 10.0, 6.0 Hz, 1$H_b$), 3.40 (dd, *J* = 10.0, 6.8 Hz, 1$H_a$), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.03 (m, 1H, 4-H), 1.83 (m, 1H, 2-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.02 (s, 9H, C($CH_3$)$_3$), 0.93 (d, *J* = 6.7 Hz, 3H, 6-$CH_3$), 0.88 (d, *J* = 6.9 Hz, 3H, , 7-$CH_3$), 0.07 (s, 9H, , 3 × Si-$CH_3$).

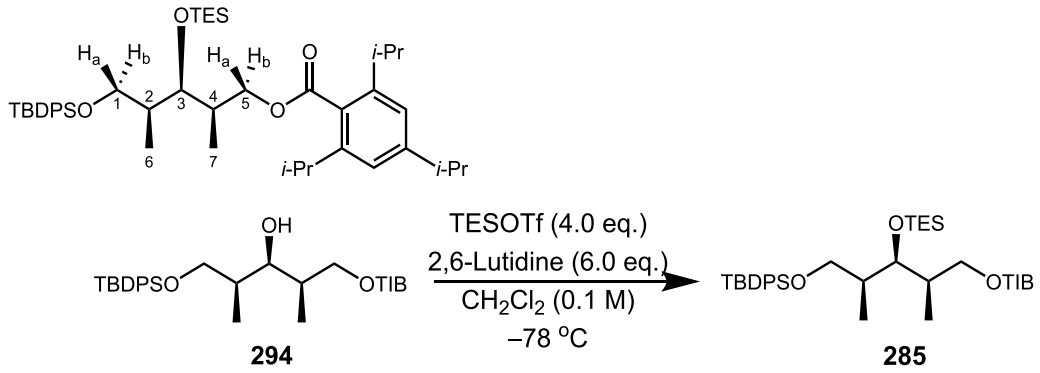
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.1 (C=O) , 150.0 (Ar-C), 144.7 (Ar-C), 135.5 (Ar-C), 133.6 (Ar-C), 130.7 (Ar-C), 129.6 (Ar-C), 127.6 (Ar-C), 120.8 (Ar-C), 72.6 (3-C) 66.8 (1-C), 65.4 (5-C), 35.4 (2-C), 34.4 (4-C), 31.5 (*C*H($CH_3$)$_2$), 26.8 (3C, C(*C*$H_3$)$_3$), 24.2 (CH(*C*$H_3$)$_2$), 24.1 (CH(*C*$H_3$)$_2$), 24.0 (CH(*C*$H_3$)$_2$), 19.3 (*C*($CH_3$)$_3$), 14.1 (7-C), 14.0 (6-C), 0.7 (3C, 3 × Si-$CH_3$).

**HRMS** (ESI) calc'd for $C_{42}H_{64}O_4Si_2Na$ $[M+Na]^+$: 711.4241; found: 711.4237.

$[\alpha]_D^{20}$ = +19.0 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 2959, 1726, 1590, 1428, 1462, 1250, 1105, 1071, 876, 824, 773, 739, 701, 613, 504.

**(*2R,3S,4S*)-5-((tert-butyldiphenylsilyl)oxy)-2,4-dimethyl-3-((triethylsilyl)oxy)pentyl 2,4,6-triisopropylbenzoate (285)**




To a solution of alcohol **294** (102 mg, 0.17 mmol) in $CH_2Cl_2$ (1.7 mL) at –78 °C were added successively 2,6-lutidine (0.12 mL, 0.99 mmol) and TESOTf (0.15 mL, 0.66 mmol). The reaction mixture was stirred for 1 hr at –78 °C. A saturated aqueous solution of $NaHCO_3$ was added, the two phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ 3 times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (ethyl acetate : petroleum ether: 0.03) on silica gel to afford compound **285** (107 mg, 89 %) as a colourless oil.

**$R_f$**: 0.77 (ethyl acetate : petroleum ether: 0.05).

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.94 – 7.87 (m, 1H, Ar-H), 7.66 (m, 4H, Ar-H), 7.02 (s, 1H, Ar-H), 4.37 (dd, *J* = 10.6, 4.7 Hz, 1H, 5-$H_b$), 4.12 (dd, *J* = 10.6, 8.9 Hz, 1H, 5-$H_a$), 3.88 (dd, *J* = 10.4, 6.3 Hz, 1H, 3-H), 3.55 (dd, *J* = 9.8, 7.0 Hz, 1H, 1-$H_a$), 3.42 (dd, *J* = 9.8, 6.6 Hz, 1H, 1-$H_b$), 2.88 (hept, *J* = 7.0 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.17 – 2.05 (m, 1H, CH), 1.92 – 1.81 (m, 1H, CH), 1.26 (d, *J* = 7.0 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.05 (s, 9H, C$(CH_3)_3$), 0.97 (d, *J* = 6.8 Hz, 3H, $CH_3$), 0.94 (t, *J* = 7.9 Hz, 9H, 3 × TES-$CH_3$), 0.89 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.58 (q, *J* = 7.9 Hz, 6H, 3 × Si-$CH_2$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.8 (Ar-C), 135.9 (Ar-C), 135.6 (Ar-C), 130.7 (Ar-C), 129.6 (Ar-C), 127.6 (Ar-C), 120.8 (Ar-C), 73.4 (3-C), 68.0 (5-C), 66.8 (1-C), 38.1 (2-C), 38.0 (4-C), 34.4 (*C*H$(CH_3)_2$), 31.6 (2C, 2 ×

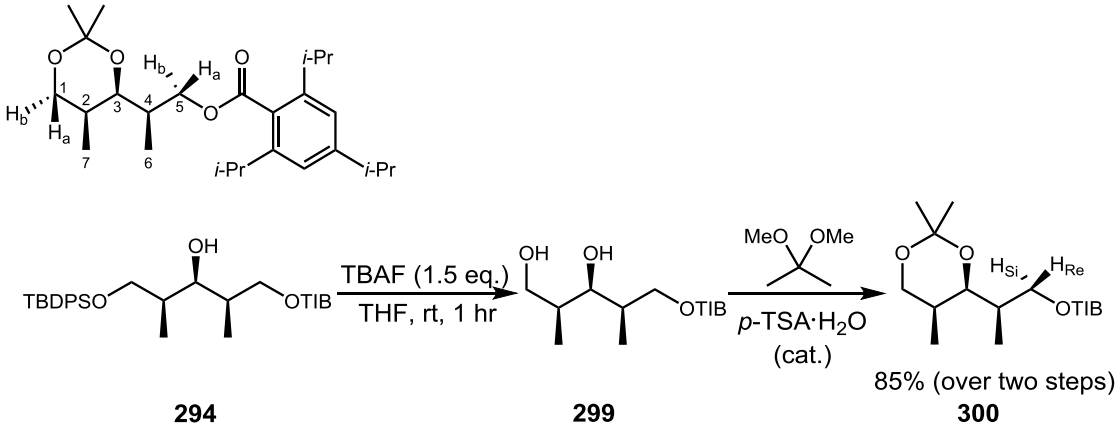
*C*H($CH_3$)$_2$), 27.0 (3C, C(*C*H$_3$)$_3$), 26.1 (3C, C(*C*H$_3$)$_3$), 24.2 (CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 24.0 (CH(*C*H$_3$)$_2$), 19.1 (*C*(CH$_3$)$_3$), 13.5(CH$_3$), 12.1 (CH$_3$), 7.0 (Si-CH$_2$), 5.3 (Si-CH$_2$).

**HRMS** (ESI) calc'd for $C_{45}H_{70}O_4Si_2Na$ $[M+Na]^+$: 753.4705; found: 753.4702.

$[\alpha]_D^{20}$ = +2.7 (c 1.1, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$ : 2959, 1726, 1461, 1428, 1250, 1105, 1073, 876, 823, 738.

**(*R*)-2-((*4R,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (300)**




**294** **299** **300**

A solution of TBAF (1.0 M in THF) (2.8 mL, 2.77 mmol) was added dropwise to a solution of benzoate ester **294** (1.14 g, 1.85 mmol) in anhydrous THF (18.0 mL). The colourless mixture was then stirred at rt for 1.0 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in 2, 2-dimethoxypropane (3.41 mL, 27.7 mmol) was added *p*-toluenesulfonic acid monohydrate (3.5 mg). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuo and purified through flash chromatography

on silica gel (ethyl acetate : hexane = 1:20) to afford benzoate ester **300** (631.7 mg, 85%) as a colourless oil.

**$R_f$**: 0.91 (ethyl acetate : hexane = 1:10)

**$^1$H NMR** (301 MHz, Chloroform-d) δ 7.01 (s, 2H, 2 × Ar-H), 4.26 (dd, *J* = 11.2, 3.4 Hz, 1H, 5-$H_b$), 4.17 (dd, *J* = 11.5, 5.2 Hz, 1H, 5-$H_a$), 4.04 (dd, *J* = 11.5, 2.8 Hz, 1H, 3-H), 3.74 (dd, *J* = 10.0, 2.3 Hz, 1H, 1-$H_a$), 3.60 (dd, *J* = 10.0, 1.6 Hz, 1H, 1-$H_b$), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$)), 1.96 (m, 1H, 4-H), 1.58 (m, 1H, 2-H), 1.38 (s, 6H, 2 × $CH_3$), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.13 (d, *J* = 6.9 Hz, 3H, 6-$CH_3$), 1.06 (d, *J* = 6.7 Hz, 3H, 7-$CH_3$).

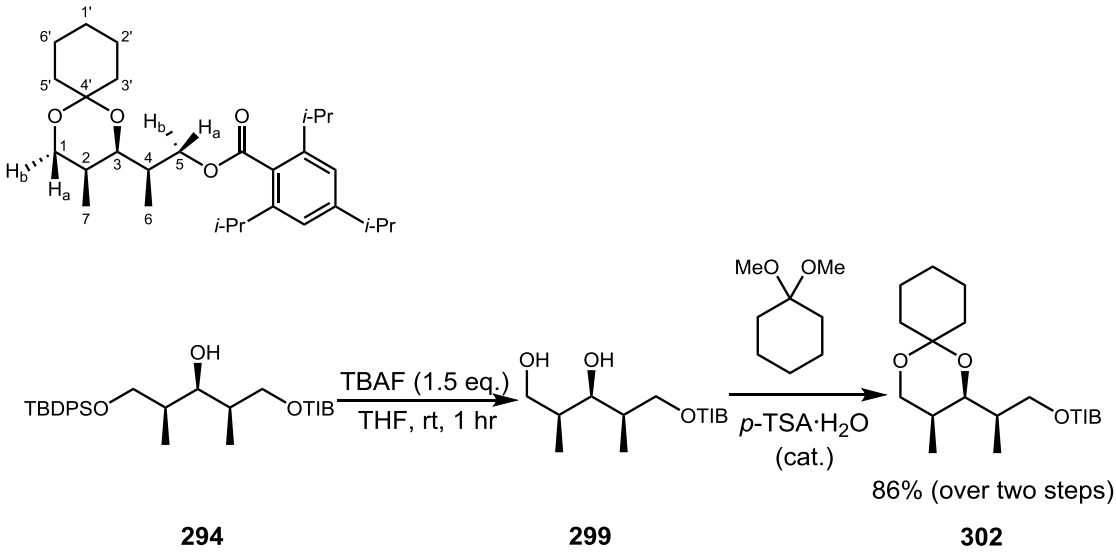
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.7 (Ar-C), 130.4 (Ar-C), 120.9 (Ar-C), 98.8 ((-O)$_2$*C*($CH_3$)$_2$), 73.1 (5-C), 66.9 (3-C), 66.0 (1-C), 34.4 (4-C), 34.3 (2-C), 31.7 (*C*H($CH_3$)$_2$), 30.3 (*C*H($CH_3$)$_2$), 29.7 (*C*H($CH_3$)$_2$), 24.3 (CH(*C*H$_3$)$_2$), 24.2 (CH(*C*H$_3$)$_2$), 23.9 (CH(*C*H$_3$)$_2$), 14.2 (6-$CH_3$), 10.8 (7-$CH_3$).

**HRMS** (ESI) calc'd for $C_{26}H_{42}NaO_4$ $[M+Na]^+$: 441.2975; found: 441.2975.

$[\alpha]_D^{20}$ = –9.1 (c 1.1, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2962, 1725, 1606, 1461, 1380, 1241, 1176, 1102, 1068, 1008, 963, 876, 524.

**(*R*)-2-((*2R,3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)propyl 2,4,6-triisopropylbenzoate (302)**



A solution of TBAF (1.0 M in THF) (2.4 mL, 2.38 mmol) was added dropwise to a solution of benzoate ester **302** (979 mg, 1.59 mmol) in anhydrous THF (15.9 mL). The colourless mixture was then stirred at rt for 1.0 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in 1,1-dimethoxycyclohexane (3.58 mL, 23.8 mmol) was added *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuo and purified through flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to afford benzoate ester **302** (624.7 mg, 86%).

**R**$_f$: 0.50 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.02 (s, 2H, 2 × Ar-H), 4.28 (dd, *J* = 11.3, 3.3 Hz, 1H, 5-$H_b$), 4.18 (dd, *J* = 11.3, 5.2 Hz, 1H, 5-$H_a$), 4.11 (dd, *J* = 11.5, 2.7 Hz, 1H, 3-H), 3.75 (dd, *J* = 9.8, 2.3 Hz, 1H, 1-$H_a$), 3.58 (dd, *J* = 9.8, 1.6 Hz, 1H, 1-$H_b$), 2.86 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.25 – 2.10 (m, 1H, 4-H), 2.01 – 1.96 (m, 1H, 2-H), 1.75 – 1.35 (m, 10H, 5 × Cy-C*H*$_2$), 1.25 (d, 18H, 3 × CH(C*H*$_3$)$_2$), 1.15 (d, *J* = 6.9 Hz, 3H, 6-$CH_3$), 1.12 (d, *J* = 6.7 Hz, 3H, 7-$CH_3$).

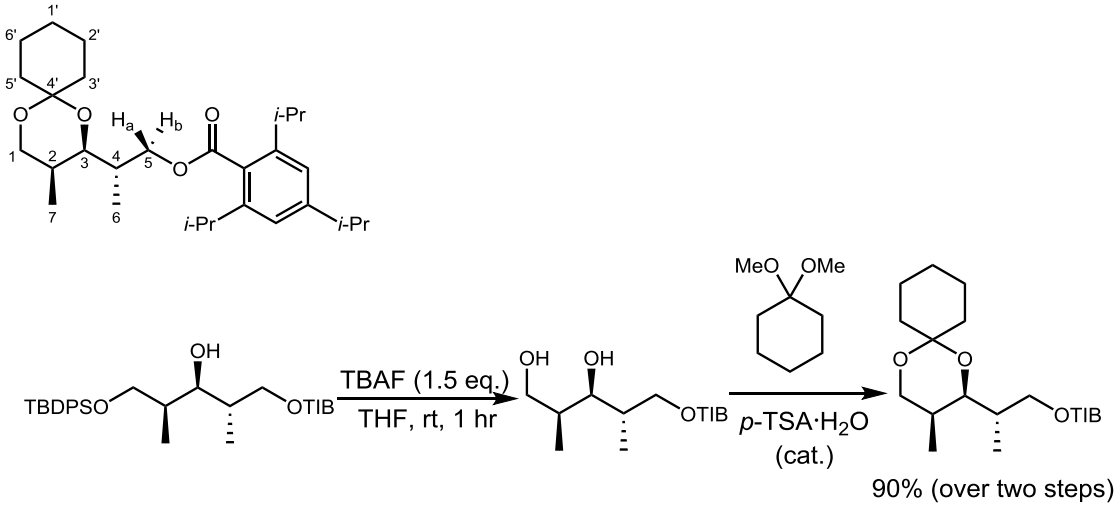
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.8 (C=O), 150.1 (Ar-C), 144.7 (Ar-C), 130.5 (Ar-C), 120.9 (Ar-C), 98.8 (O-C-O), 72.0 (3-C), 66.1 (5-C), 66.0 (1-C), 38.6 (Cy-$CH_2$), 34.4 (CH), 34.3 (*C*H$(CH_3)_2$) 31.7 (2 × *C*H$(CH_3)_2$), 30.5 (CH), 27.5 (Cy-*C*$H_2$), 25.8 (Cy-*C*$H_2$), 24.2 (CH(*C*$H_3$)$_2$), 24.1 (CH(*C*$H_3$)$_2$), 23.9 (CH(*C*$H_3$)$_2$), 22.6 (Cy-$CH_2$), 22.4 (Cy-$CH_2$), 14.5 ($CH_3$), 11.0 ($CH_3$).

**HRMS** (ESI) calc'd for $C_{29}H_{46}NaO_4$ $[M+Na]^+$: 481.3288; found: 481.3286.

$[\alpha]_D^{20}$ = –6.6 (c 1.1, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2962, 1726, 1607, 1467, 1363, 1102, 996, 448.

**(*S*)-2-((*2R*,*3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)propyl 2,4,6-triisopropylbenzoate (343)**




**309a** **343**

A solution of TBAF (1.0 M in THF) (3.0 mL, 3.0 mmol) was added dropwise to a solution of benzoate ester **309a** (1.23 g, 2.0 mmol) in anhydrous THF (20 mL). The colourless mixture was then stirred at rt for 1.0 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in 1,1-dimethoxycyclohexane (3 mL) was added *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuo and purified through flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to afford benzoate ester **343** (823 mg, 90%).

**$R_f$**: 0.75 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-CH), 4.43 (dd, *J* = 10.8, 3.4 Hz, 1H, 5-$H_a$), 4.33 (dd, *J* = 10.8, 5.8 Hz, 1H, 5-$H_b$), 4.10 (ddd, *J* = 11.5, 2.3 Hz, 1H, 1-H),

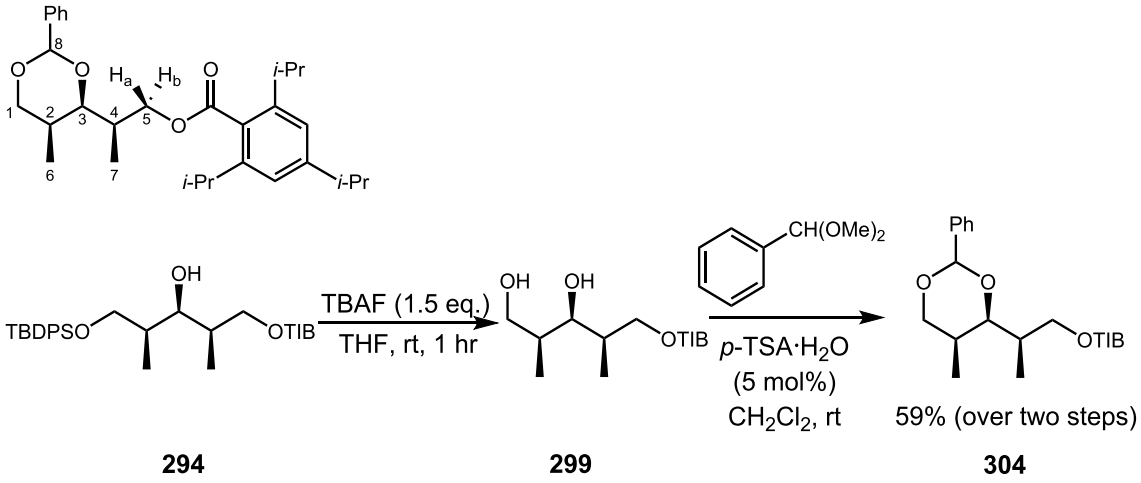
3.76 (dd, *J* = 10.1, 2.3 Hz, 1H, 3-H), 3.59 (dd, *J* = 11.5, 1.6 Hz, 1H, 1-H), 2.87 (hept, *J* = 6.9 Hz, 3H), 1.96 (m, 2H, CH + 1 Cy-$CH_2$), 1.89 – 1.29 (m, 10H, CH + 9 × Cy-$CH_2$), 1.26 (d, *J* = 6.9 Hz, 18H, 3 × CH(C$H_3$)$_2$), 1.09 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.93 (d, *J* = 6.9 Hz, 3H, $CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 150.1 (Ar-C), 144.9 (Ar-C), 130.9 (Ar-C) 120.9 (Ar-CH), 98.8 (O-C-O), 71.3 (3-C), 67.0 (5-C), 66.4 (1-C), 38.7 (Cy-$CH_2$), 34.6 (CH), 34.5 (*C*H(C$H_3$)$_2$), 31.6 (2 × *C*H(C$H_3$)$_2$), 29.9 (CH), 27.8 (Cy-$CH_2$), 25.9 (Cy-$CH_2$), 24.5 (CH(*C*$H_3$)$_2$), 24.3 (CH(*C*$H_3$)$_2$), 24.0 (CH(*C*$H_3$)$_2$), 22.8 (Cy-$CH_2$), 22.7 (Cy-$CH_2$), 12.2 ($CH_3$), 10.4 ($CH_3$).

$[\alpha]_D^{20}$ = –40 (c 0.2, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2962, 2867, 1724, 1607, 1463, 1364, 1284, 1252, 1103, 1056, 1000, 963, 875.

**(*2R*)-2-((4R,5S)-5-methyl-2-phenyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (304)**




**294** **299** **304**

A solution of TBAF (0.75 mL, 1.0 M in THF, 0.75 mmol) was added dropwise to a solution of benzoate ester **294** (308.5 mg, 0.5 mmol) in anhydrous THF (5 mL). The colourless mixture was then stirred at rt for 1.0 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol **299** as colourless oil without further purification.

To a solution of the crude diol from last step and (dimethoxymethyl)benzene (84 mg, 0.55 mmol) in $CH_2Cl_2$ (2.5 mL) was added *p*-toluenesulfonic acid monohydrate (4.8 mg, 0.025 mmol). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to afford benzoate ester **304** (139 mg, 59%).

**$R_f$**: 0.55 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.60 – 7.49 (m, 2H, Ar-CH), 7.45 – 7.32 (m, 3H, Ar-CH), 7.08 (d, *J* = 10.1 Hz, 2H, Ar-CH), 5.53 (s, 1H, 8-H), 4.37 (dd, *J* = 11.2, 3.3 Hz, 1H, 5-$H_a$), 4.28 (dd, *J* = 11.2, 5.1 Hz, 1H, 5-$H_b$), 4.09 (d, *J* = 1.6 Hz, 2H, 1-H), 3.84 (dd, *J* = 9.8, 2.1 Hz, 1H, 3-H), 2.92 (hept, *J* = 6.9 Hz, 3H, C*H*$(CH_3)_2$), 2.27 – 2.12 (m, 1H, CH), 1.83 – 1.70 (m, 1H, CH), 1.32 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.32 (d, *J* = 7.1 Hz, 3H, $CH_3$), 1.24 (d, *J* = 6.7 Hz, 3H, $CH_3$).

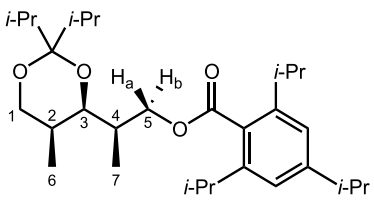
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.2 (C=O), 150.3 (Ar-C), 144.8 (Ar-C), 138.9 (Ar-C), 130.5 (Ar-C), 128.8 (Ar-CH), 128.3 (Ar-CH), 126.0 (Ar-CH), 121.0 (Ar-CH), 102.0 (8-C), 81.3 (3-C), 73.8 (1-C), 66.0 (5-C), 34.5 (*C*H$(CH_3)_2$), 34.4 (CH), 31.8 (2 × *C*H$(CH_3)_2$), 30.5 (CH), 24.4 (CH(*C*H$_3)_2$), 24.3 (CH(*C*H$_3)_2$), 24.0 (CH(*C*H$_3)_2$), 14.4 ($CH_3$), 11.5 ($CH_3$).

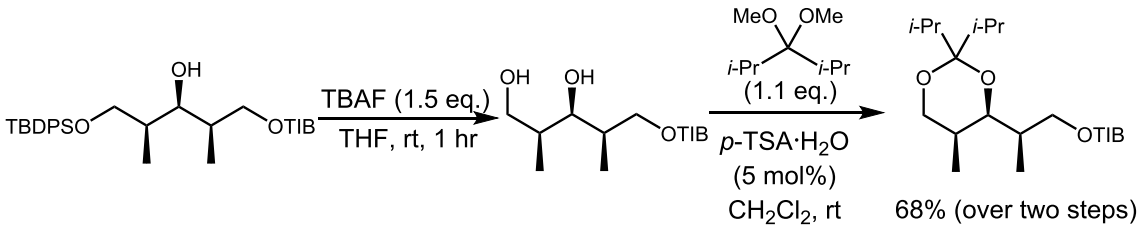
HRMS (ESI) calc'd for $C_{30}H_{42}NaO_4$ [M+Na]+: 489.2981; found: 489.2983.

$[\alpha]_D^{20}$ = –35.1 (c 0.86, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2959, 2924, 2868, 1728, 1604, 1463, 1363, 1252, 1139, 1112, 1076, 1029, 1018, 974, 877, 755, 699.

**(*R*)-2-((4R,5S)-2,2-diisopropyl-5-methyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (305)**






**294** **299** **305**

A solution of TBAF (1.0 mL, 1.0 M in THF, 1.0 mmol) was added dropwise to a solution of benzoate ester **294** (616 mg, 1.0 mmol) in anhydrous THF (10 mL). The colourless mixture was then stirred at rt for 1 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step and 3,3-dimethoxy-2,4-dimethylpentane (176.3 mg, 1.1 mmol) in $CH_2Cl_2$ (5 mL) was added *p*-toluenesulfonic acid monohydrate (9.5 mg). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:30) to afford benzoate **305** (325 mg, 68%).

**$R_f$**: 0.95 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.01 (d, *J* = 6.0 Hz, 2H, Ar-CH), 4.35 (dd, *J* = 11.1, 5.4 Hz, 1H, 5-$H_a$), 4.15 (dd, *J* = 11.1, 5.9 Hz, 1H, 5-$H_b$), 3.74 (dd, *J* = 6.5, 4.2 Hz, 1H, 3-H), 3.69 (d, *J* = 4.7 Hz, 2H, 1-H), 2.82 (hept, *J* = 6.9 Hz, 5H, 3 × C*H*$(CH_3)_3$ + 2 × C*H*$(CH_3)_3$), 2.12 – 2.04 (m, 1H, CH), 1.91 – 1.82 (m, 1H, CH), 1.24 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_3$), 1.10 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.08 (d, *J* = 6.9 Hz, 12H, 2 × CH(C*H*$_3)_3$), 1.05 (d, *J* = 7.0 Hz, 3H, $CH_3$).

**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.4 (C=O), 150.3 (Ar-C), 144.9 (Ar-C), 130.5 (Ar-C), 121.0 (Ar-CH), 100.9 (O-C-O), 74.9 (3-C), 67.6 (5-C), 67.4 (1-C), 39.0 (2 × *C*H$(CH_3)_2$), 37.4 (CH), 36.0 (CH), 34.6 (*C*H$(CH_3)_2$), 31.8 (2 × *C*H$(CH_3)_2$), 24.4

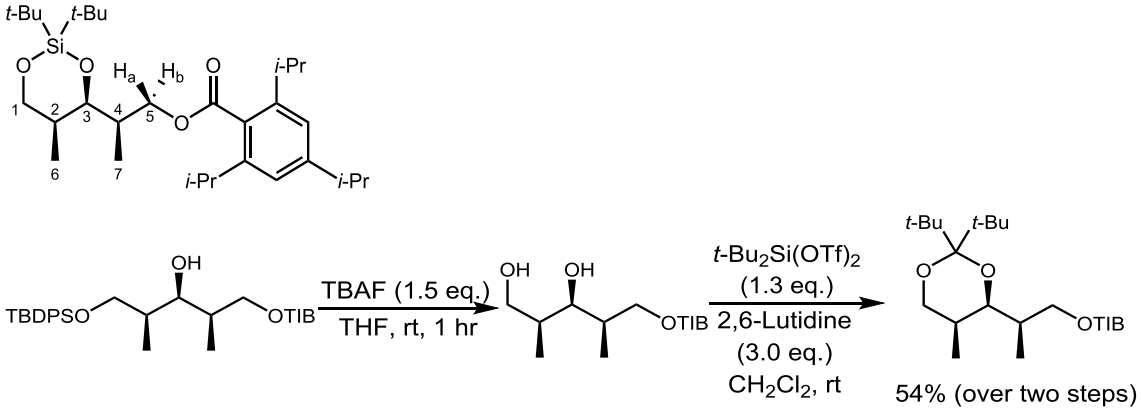
($CH(CH_3)_2$), 24.3 ($CH(CH_3)_2$) 24.1 ($CH(CH_3)_2$), 18.7 (2 × $CH(CH_3)_2$), 12.9 ($CH_3$), 11.0 ($CH_3$).

**HRMS (ESI)** calc'd for $C_{30}H_{50}NaO_4$ [M+Na]+: 497.3607; found: 497.3605.

$[\alpha]_D^{20}$ = –4.1 (c 0.98, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2961, 2928, 2869, 1726, 1606, 1461, 1384, 1250, 1136, 1104, 1068, 1036, 982.

**(*R*)-2-((*4S*,*5S*)-2,2-di-tert-butyl-5-methyl-1,3,2-dioxasilinan-4-yl)propyl 2,4,6-triisopropylbenzoate (306)**




A solution of TBAF (1.0 mL, 1.0 M in THF, 1.0 mmol) was added dropwise to a solution of benzoate ester **294** (616 mg, 1.0 mmol) in anhydrous THF (10 mL). The colourless mixture was then stirred at rt for 1 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step and *t*-$Bu_2Si(OTf)_2$ (0.8 mL, 1.04 g, 2.36 mmol) in $CH_2Cl_2$ (1.13 mL) was added 2, 6-lutidine (0.64 mL, 583 mg, 5.44 mmol). The reaction was stirred for 12 hrs at 45 ˚C. After that the reaction mixture was diluted with $CH_2Cl_2$ (10 mL), washed with saturated aqueous solution of $NaHCO_3$ (5 mL), aqueous solution of $NaHSO_4$ (2 × 5 mL), brine (5 mL). The organic layer was dried

over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:30) to afford benzoate **306** (504 mg, 54%).

**$R_f$**: 0.96 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-H), 4.31 (dd, *J* = 11.3, 2.8 Hz, 1H, 5-$H_a$), 4.25 (dd, *J* = 11.1, 4.2 Hz, 1H, 1-$H_b$), 4.15 (dd, *J* = 11.1, 5.6 Hz, 1H, 1-$H_a$), 4.16 – 4.11 (m, 1H, 3-H), 3.91 (dd, *J* = 11.3, 2.2 Hz, 1H, 5-$H_b$), 2.89 (hept, *J* = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 2.80 (hept, *J* = 6.8 Hz, 2H, 2 × C*H*$(CH_3)_2$), 2.03 – 1.94 (m, 1H, 2-H), 1.84 – 1.76 (m, 1H, 4-H), 1.24 (d, *J* = 6.8 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.19 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.15 (d, *J* = 6.7 Hz, 3H, $CH_3$), 1.06 (s, C(C*H*$_3)_3$), 1.04 (s, C(C*H*$_3)_3$).

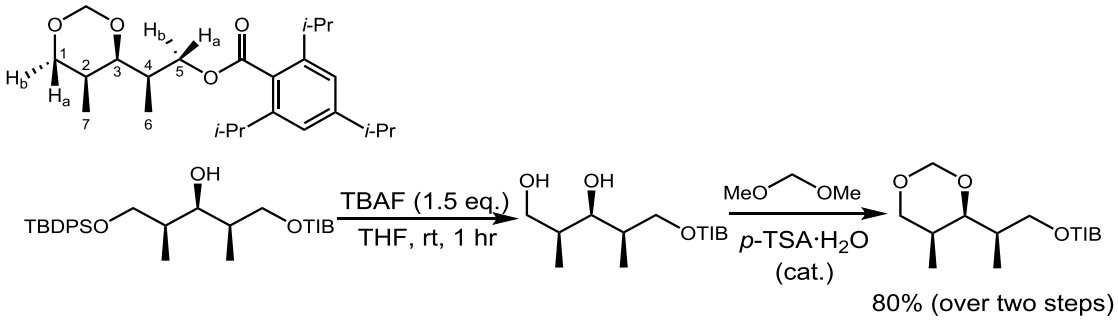
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.2 (C=O), 150.1 (Ar-C), 144.7 (Ar-C), 130.5 (Ar-C), 120.8 (Ar-*C*H), 77.2 (3-C), 71.1 (5-C), 66.7 (1-C), 37.0 (2-C), 35.4 (4-C), 34.4 (9-*C*H$(CH_3)_2$), 31.6 (8-*C*H$(CH_3)_2$), 28.6 (8-*C*H$(CH_3)_2$), 27.5 (8-*C*H$(CH_3)_2$), 24.2 (8,9-CH(*C*H$_3)_2$), 23.9 (8,9-CH(*C*H$_3)_2$), 23.4 (10-*C*$(CH_3)_3$), 20.7 (10-*C*$(CH_3)_3$), 14.0 (6-C), 11.3 (7-C).

**HRMS (ESI)** calc'd for $C_{31}H_{54}NaO_4Si$ [M+Na]+: 541.3689; found: 541.3685.

$[\alpha]_D^{20}$ = –15.7 (c 0.9, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2960, 2926, 2868, 1726, 1607, 1461, 1364, 1250, 1136, 1111, 967, 503.

**(*R*)-2-((*4R,5S*)-5-methyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (312)**




**294** **299** **312**

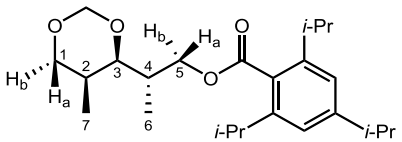
A solution of TBAF (1.04 mL, 1.0 M in THF, 1.04 mmol) was added dropwise to a solution of benzoate ester **294** (394 mg, 1.04 mmol) in anhydrous THF (10 mL). The colourless mixture was then stirred at rt for 1. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was

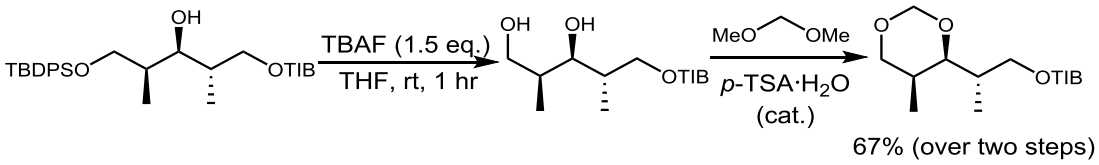
extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in dimethoxymethane (2 mL, 22.6 mmol) was added *p*-toluenesulfonic acid monohydrate (9.9 mg). The reaction was stirred for 12 hrs at 50 °C. After that the reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography (ethyl acetate : petroleum ether = 1:30) on silica gel to afford benzoate ester **312** (323.4 mg, 80%).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-H), 5.06 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.65 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.26 (dd, *J* = 11.3, 3.4 Hz, 1H, 5-$H_b$), 4.17 (dd, *J* = 11.3, 5.1 Hz, 1H, 5-$H_a$), 3.88 (dd, *J* = 11.2, 1.3 Hz, 1H, 1-H), 3.77 (dd, *J* = 11.2, 2.6 Hz, 1H, 1-H), 3.50 (dd, *J* = 9.8, 2.3 Hz, 1H, 3-H), 2.84 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.06 – 2.01 (m, 1H, CH), 1.71 – 1.60 (m, 1H, CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.20 (d, *J* = 6.9 Hz, 3H, $CH_3$), 1.11 (d, *J* = 6.7 Hz, 3H, $CH_3$).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 150.4 (Ar-C), 144.8 (Ar-C), 130.5 (Ar-C), 121.1 (Ar-CH), 94.9 (O-C-O), 81.0 (O-C), 73.5 (O-C), 65.9 (O-C), 34.6 (*C*H$(CH_3)_2$), 34.4 (CH), 31.8 (2 × *C*H$(CH_3)_2$), 31.3 (CH), 24.4 (CH(*C*H$_3)_2$), 24.3 (CH(*C*H$_3)_2$), 24.1 (CH(*C*H$_3)_2$), 14.4 ($CH_3$), 11.4 ($CH_3$).
**HRMS** (ESI) calc'd for $C_{24}H_{38}NaO_4$ $[M+Na]^+$: 413.2668; found: 413.2665.
$[\alpha]_D^{20}$ = +11.8 (c 1.0, $CHCl_3$).
**IR** $\nu_{max}$ (neat)/cm$^{-1}$ : 2962, 1725, 1607, 1461, 1386, 1249, 1168, 1104, 1068, 1015, 993, 876.

**(*S*)-2-((*4R,5S*)-5-methyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (313)**






**309a** **310a** **313**

A solution of TBAF (0.91 mL, 1.0 M in THF, 0.91 mmol) was added dropwise to a solution of benzoate ester **309a** (374 mg, 0.61 mmol) in anhydrous THF (6.1 mL). The colourless mixture was then stirred at rt for 1 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

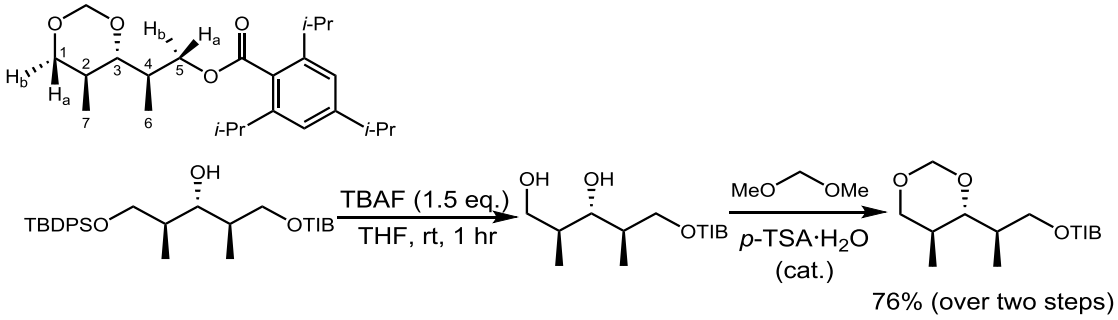
To a solution of the crude diol from last step in dimethoxymethane (2 mL, 22.6 mmol) was added *p*-toluenesulfonic acid monohydrate (5.8 mg, 0.03 mmol). The reaction was stirred for 12 hrs at 50 $^oC$. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography ethyl acetate/petroleum ether = 1:20) on silica gel to afford benzoate ester **313** (159.8 mg, 67%).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-H), 5.05 (d, *J* = 6.0 Hz, 1H, $OCH_2O$), 4.65 (d, *J* = 6.0 Hz, 1H, $OCH_2O$), 4.36 (dd, *J* = 11.3, 3.4 Hz, 1H, 5-Ha), 4.35 (dd, *J* = 11.3, 5.1 Hz, 1H, 5-$H_b$), 3.89 (dd, *J* = 11.2, 1.3 Hz, 1H, 1-H), 3.79 (dd, *J* = 11.2, 2.5 Hz, 1H, 1-H), 3.51 (dd, *J* = 10.3, 2.3 Hz, 1H, 3-H), 2.85 (hept, *J* = 7.0 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.04 – 1.97 (m, 1H, CH), 1.62 – 1.57 (m, 1H, CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.14 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.93 (d, *J* = 6.9 Hz, 3H, $CH_3$).
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 150.2 (Ar-C), 144.8 (Ar-C), 130.9 (Ar-C), 121.0 (Ar-C), 94.5 (O-C-O), 79.7 (O-C), 73.7 (O-C), 66.8 (O-C), 34.6 (*C*H$(CH_3)_2$), 34.3 (CH), 31.7 (2 × *C*H$(CH_3)_2$), 30.5 (CH), 24.4 (CH(*C*H$_3)_2$), 24.3 (CH(*C*H$_3)_2$), 24.1 (CH(*C*H$_3)_2$), 12.3 ($CH_3$), 10.7 ($CH_3$).
**HRMS** (ESI) calc'd for $C_{24}H_{38}NaO_4$ $[M+Na]^+$: 413.2668; found: 413.2666.

$[\alpha]_D^{20}$ = –10.2 (c 0.07, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 2962, 1725, 1606, 1461, 1385, 1252, 1166, 1102, 1076, 1017, 985, 877.

**(*R*)-2-((*4S,5S*)-5-methyl-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (314)**




**309b** **310b** **314**

A solution of TBAF (1.0 M in THF) (1.2 mL, 1.19 mmol) was added dropwise to a solution of benzoate ester **309a** (487 mg, 0.79 mmol) in anhydrous THF (7.9 mL). The colourless mixture was then stirred at rt for 1. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in dimethoxymethane (2 mL, 22.6 mmol) was added *p*-toluenesulfonic acid monohydrate (7.6 mg, 0.039 mmol). The reaction was stirred for 12 hrs at 50 $^oC$. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography ethyl acetate : petroleum ether = 1:20) on silica gel to afford benzoate ester **314** (234 mg, 76%).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-H), 5.07 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.61 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.56 (dd, *J* = 11.1, 4.7 Hz, 1H, 5-$H_b$), 4.12 (dd, *J* = 11.1, 8.6 Hz, 1H, 5-$H_a$), 3.96 (dd, *J* = 11.2, 4.6 Hz, 1H, 1-H), 3.21 (m, 2H, 1-H

+ 3-H), 2.87 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.26 – 2.21 (m, 1H, CH), 2.15 – 2.07 (m, 1H, CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.14 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.77 (d, *J* = 6.9 Hz, 3H, $CH_3$).

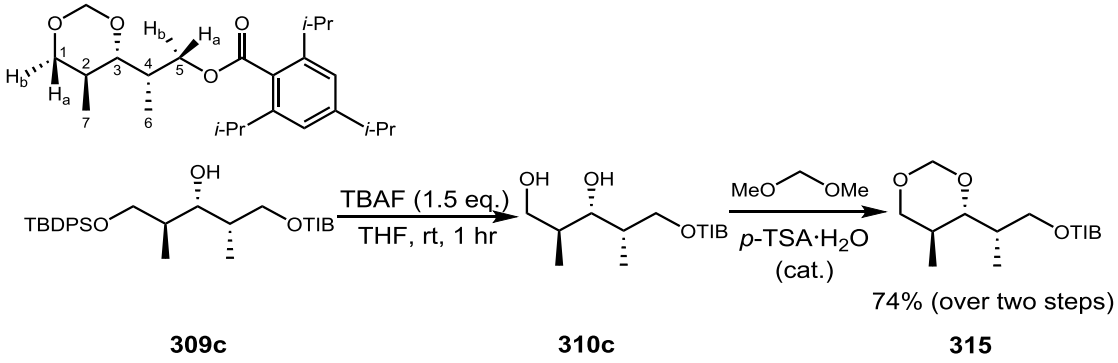
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.2 (C=O), 150.2 (Ar-C), 144.8 (Ar-C), 130.8 (Ar-C), 121.0 (Ar-CH), 94.2 (O-C-O), 85.8 (O-C), 72.9 (O-C), 66.4 (O-C), 34.6 (*C*H($CH_3$)$_2$), 33.9 (CH), 32.1 (2 × *C*H($CH_3$)$_2$), 31.7 (CH), 24.3 (2 × CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 15.7 ($CH_3$), 12.8 ($CH_3$).

**HRMS** (ESI) calc'd for $C_{24}H_{38}NaO_4$ $[M+Na]^+$: 413.2668; found: 413.2667.

$[\alpha]_D^{20}$ = +24.5 (c 0.24, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2961, 1723, 1608, 1460, 1386, 1250, 1177, 1098, 1068, 1034, 965, 876.

**(*S*)-2-((*4S,5S*)-5-methyl-1,3-dioxan-4-yl) propyl 2,4,6-triisopropylbenzoate (315)**




A solution of TBAF (1.0 M in THF) (2.4 mL, 2.38 mmol) was added dropwise to a solution of benzoate ester **309c** (979 mg, 1.59 mmol) in anhydrous THF (15.9 mL). The colourless mixture was then stirred at rt for 1. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in dimethoxymethane (2 mL, 22.6 mmol) was added *p*-toluenesulfonic acid monohydrate (9 mg, 0.03 mmol). The reaction was stirred for 12 hrs at 50 °C. After that the reaction mixture was poured into saturated

aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography ethyl acetate : petroleum ether = 1:20) on silica gel to afford benzoate ester **315** (608 mg, 74%).

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.02 (s, 2H, Ar-H), 5.07 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.61 (d, *J* = 6.1 Hz, 1H, $OCH_2O$), 4.30 (dd, *J* = 10.7, 8.8 Hz, 1H, 5-$H_b$), 4.25 (dd, *J* = 10.7, 6.1 Hz, 1H, 5-$H_a$), 3.98 (dd, *J* = 11.8, 4.8 Hz, 1H, 1-H), 3.40 (dd, *J* = 10.1, 2.1 Hz, 1H, 3-H), 3.22 (dd, *J* = 11.8, 11.0 Hz, 1H, 1-H), 2.87 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.25 – 2.17 (m, 1H, CH), 2.07 – 1.98 (m, 1H, CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.01 (d, *J* = 6.8 Hz, 3H, $CH_3$), 0.69 (d, *J* = 6.7 Hz, 3H, $CH_3$).

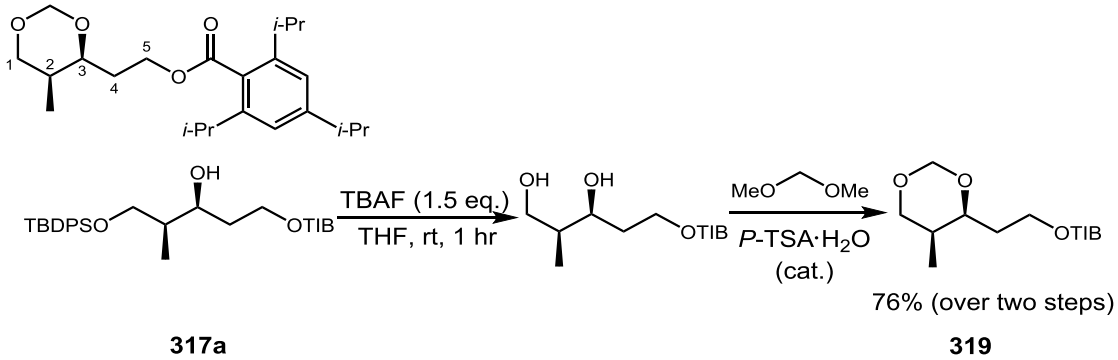
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.0 (C=O), 150.2 (Ar-C), 144.8 (Ar-C), 130.8 (Ar-C),121.0 (Ar-C), 94.0 (O-C-O), 81.7 (O-C), 72.9 (O-C), 66.9 (O-C), 34.6 (*C*H$(CH_3)_2$), 33.3 (CH), 31.7 (2 × *C*H$(CH_3)_2$), 31.2 (CH), 24.4 (2 × CH(*C*H$_3)_2$), 24.1 (CH(*C*H$_3)_2$), 12.1 ($CH_3$), 10.0 ($CH_3$).

**HRMS** (ESI) calc'd for $C_{24}H_{38}NaO_4$ $[M+Na]^+$: 413.2668; found: 413.2669.

$[\alpha]_D^{20}$ = +18.2 (c 0.6, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$ : 2960, 1724, 1606, 1461, 1384, 1249, 1167, 1098, 1066, 1034, 987, 687.

**2-((4S,5S)-5-methyl-1,3-dioxan-4-yl)ethyl 2,4,6-triisopropylbenzoate (319)**




A solution of TBAF (1.0 M in THF) (1.8 mL, 1.8 mmol) was added dropwise to a solution of benzoate ester **317a** (724 mg, 1.2 mmol) in anhydrous THF (12 mL). The colourless mixture was then stirred at rt for 1. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was

extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a flask charged with the crude diol from last step were added *p*-toluenesulfonic acid monohydrate (15 mg, 0.06 mmol) and 1,2-dimethoxymethane (2 mL). The reaction mixture was refluxed for 20 hrs. After the reaction mixture was concentrated under vacuo, and purified by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 40:1) to give benzoate ester **319** (348 mg, 76%)

**$R_f$**: 0.33 (petroleum ether: ethyl acetate = 20:1)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.02 (s, 2H, Ar-CH), 5.05 (d, *J* = 6.1 Hz, 1H, O-$CH_2$-O), 4.67 (d, *J* = 6.1 Hz, 1H, O-$CH_2$-O), 4.46 – 4.37 (m, 2H, 5-H), 3.93 – 3.77 (m, 3H, 2 × 1-H + 3-H), 2.86 (hept, 3H, 3 × C*H*($CH_3$)$_2$), 2.04 – 1.93 (m, 1H, 4-H), 1.76 (m, 1H, 4-H), 1.51 (m, 1H, 2-H), 1.26 (dd, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.16 (d, *J* = 7.0 Hz, 3H, $CH_3$).

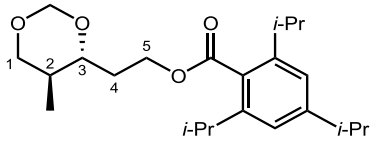
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.0 (C=O), 150.3 (Ar-C), 144.8 (Ar-C), 130.6 (Ar-C), 121.0 (Ar-C), 94.4 (O-C-O), 75.7 (O-C), 73.4 (O-C), 61.4 (O-C), 34.6 (*C*H($CH_3$)$_2$), 32.8 (CH), 32.1 (CH), 31.7 (2 × *C*H($CH_3$)$_2$), 24.3 (CH(*C*H$_3$)$_2$), 24.2 (CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 11.20 ($CH_3$).

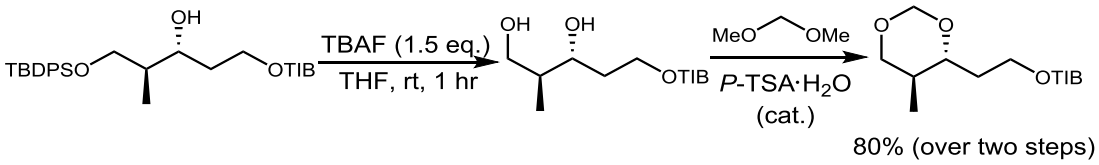
**HRMS** (ESI) calc´d for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2511; found: 399.2513.

$[\alpha]_D^{20}$ = –4.9 (*c* 0.8, $CHCl_3$)

**IR** $\nu_{max}$ ($cm^{-1}$) 2959, 2868, 1722, 1607, 1577, 1463, 1384, 1283, 1249, 1174, 1069, 1037, 959, 876, 760.

**2-((4S,5S)-5-methyl-1,3-dioxan-4-yl)ethyl 2,4,6-triisopropylbenzoate (320)**






**317b** **320**

A solution of TBAF (1.0 M in THF) (1.3 mL, 1.3 mmol) was added dropwise to a solution of benzoate ester **317b** (502 mg, 0.83 mmol) in anhydrous THF (8.3 mL). The colourless mixture was then stirred at rt for 1. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a flask charged with the crude diol from last step were added *p*-toluenesulfonic acid monohydrate (10 mg, 0.04 mmol) and 1,2-dimethoxymethane (2 mL). The reaction mixture was refluxed for 20 hrs. After the reaction mixture was concentrated under vacuo, and purified by flash column chromatography on silica gel pad (ethyl acetate : petroleum ether = 1:40) to give benzoate ester **249** (249 mg, 80%)

**$R_f$**: 0.25 (ethyl acetate : petroleum ether = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.02 (s, 2H, Ar-CH), 5.08 (dd, *J* = 6.1, 1.0 Hz, 1H, O-$CH_2$-O), 4.62 (d, *J* = 6.1 Hz, 1H, O-$CH_2$-O), 4.52 – 4.39 (m, 2H, 5-H), 3.97 (ddd, *J* = 11.2, 4.7, 1.1 Hz, 1H, 1-H), 3.35 (dd, *J* = 9.9, 2.4 Hz, 1H, 3-H), 3.22 (dd, *J* = 11.2, 11.1 Hz, 1H, 1-H), 2.88 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.21 – 2.11 (m, 1H, 2-H), 1.88 – 1.75 (m, 2H, 4-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 0.74 (d, *J* = 6.7 Hz, 3H, $CH_3$).

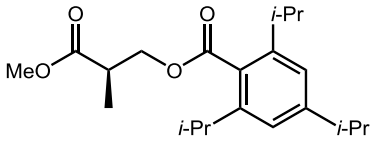
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.0 (C=O), 150.3 (Ar-C), 144.8 (Ar-C), 130.7 (Ar-C), 121.0 (Ar-CH), 93.8 (O-C-O), 79.3 (O-C), 72.6 (O-C), 61.1 (O-C), 35.0 (CH), 34.5 (*C*H$(CH_3)_2$), 32.0 (CH), 31.6 (2 × *C*H$(CH_3)_2$), 24.3 (2 × CH(*C*H$_3)_2$), 24.1 (CH(*C*H$_3)_2$), 12.6 ($CH_3$).

**HRMS** (ESI) calc´d for $C_{38}H_{54}O_4SiNa$ $[M+Na]^+$ 625.3689; found: 625.3693.

$[\alpha]_D^{20}$ = +4.0 (*c* 1.0, $CHCl_3$)

**IR** $\nu_{max}$ ($cm^{-1}$) 2960, 2870, 1724, 1606, 1575, 1461, 1363, 1283, 1250, 1176, 1075, 1035, 957 876, 759.

**(R)-3-methoxy-2-methyl-3-oxopropyl 2,4,6-triisopropylbenzoate (321)**




To a solution of (*R*)-Roche ester (3.90 g, 33.0 mmol), $PPh_3$ (8.66 g, 33.0 mmol), and TIBOH (7.45 g, 30.0 mmol) in THF (30 ml) was added DIAD (6.67 g, 33.0 mmol) dropwise at 0 °C. The solution was allowed to warm up to room temperature and stirred for 17 hrs at this temperature. Pentane (30 ml) was added and the formed precipitate was filtered off until a clear solution is obtained. After the solvents were removed under vacuum the crude was purified by flash chromatography on silica gel (petroleum ether : ethyl acetate = 20:1) to afford **321** (8.84 g, 85%).

**$R_f$:** 0.68 (petroleum ether : ethyl acetate = 5:1).

**$^1$H-NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 4.49 (dd, *J* = 10.9, 7.4 Hz, 1H, $CH_2$), 4.38 (dd, *J* = 10.9, 5.3 Hz, 1H, $CH_2$), 3.69 (s, 3H, $OCH_3$), 2.96 – 2.83 (m, 1H, CH), 2.87 (hept, *J* = 6.8 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 1.27 (d, *J* = 7.3 Hz, 3H, $CH_3$), 1.24 (d, *J* = 6.8 Hz, 18H, 3 × CH(C*H*$_3$)$_2$).

**$^{13}$C-NMR** (101 MHz, Chloroform-d) δ 174.2 (C=O), 170.8 (C=O), 150.3 (Ar-C), 145.0 (Ar-C), 130.3 (Ar-C), 121.0 (Ar-CH), 66.3 ($OCH_2$), 52.1 ($OCH_3$), 39.1 (CH), 34.6 (*C*H($CH_3$)$_2$), 31.7 (2 × *C*H($CH_3$)$_2$), 24.3 (2 × CH(*C*H$_3$)$_2$), 24.1 (2 × CH(*C*H$_3$)$_2$), 14.2 ($CH_3$).

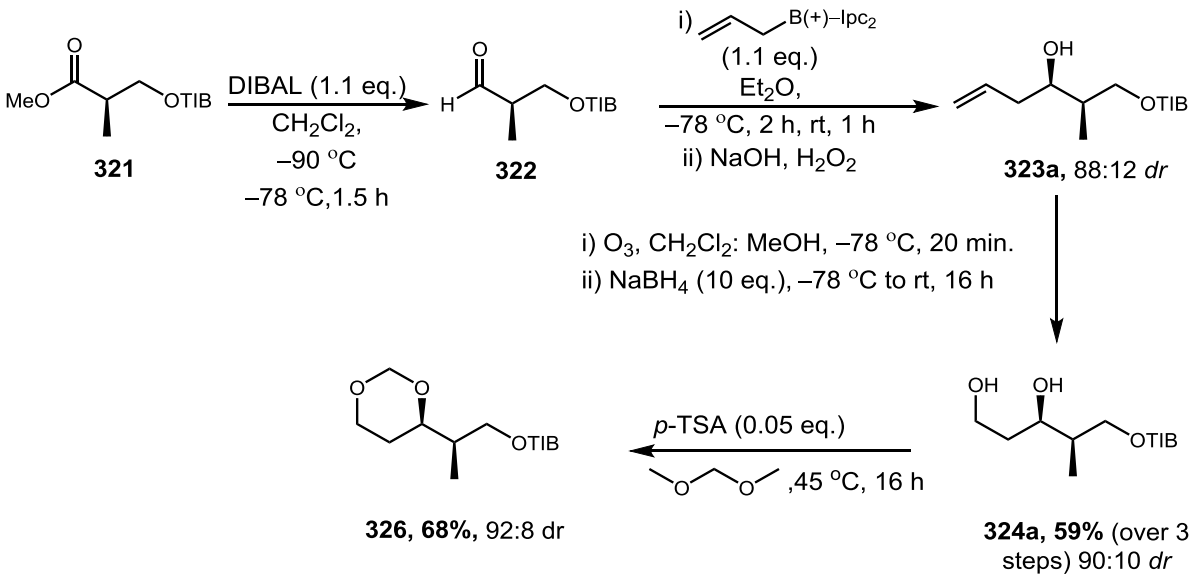
**HRMS** (ESI) calcd. for $C_{21}H_{32}O_4Na$ $[M+Na]^+$ : 371.2193; found: 371.2298.

**m.p.**= 40-42 °C.

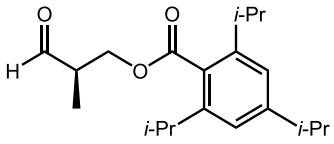
**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2961, 2870, 1723, 1606, 1577, 1453, 1288, 1251, 1135, 1071, 963, 863.

$[\alpha]_D^{20}$ = –13 (1.0, $CHCl_3$).

**Synthesis of benzoate ester 326.**

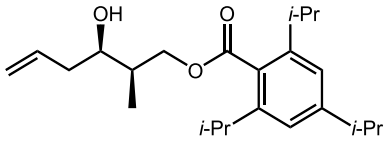



**(*R*)-2-methyl-3-oxopropyl 2,4,6-triisopropylbenzoate (322)**



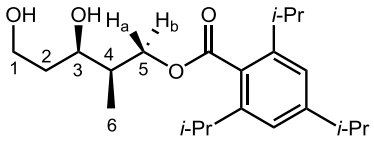

Ester **321** (1.31 g, 3.8 mmol) was stirred in $CH_2Cl_2$ (13 mL) and the solution was cooled to –90°C. DIBAL (1.0 M in hexanes, 4.1 mL, 4.1 mmol) was cooled to –90 °C and added dropwise. After addition of DIBAL the solution was transfer to cooling bath at –78°C and stirred for 90 min. Water (0.15 mL) was slowly added at –78°, followed by 15% NaOH solution (0.15 mL) and again water (0.41 mL). After warming up to room temperature the mixture was stirred for additional 30 min and $MgSO_4$ was added subsequently and the mixture stirred for another 30 min at rt. The precipitated salts were removed by filtration through celite using $Et_2O$ as eluent and solvent was removed under reduced pressure. Due to the instability of the aldehyde, the crude product was used in the next step without further purification.

**(*2R,3R*)-3-hydroxy-2-methylhex-5-en-1-yl 2,4,6-triisopropylbenzoate (323a)**




(+)-Diisopinocampheylmethoxyborane ($Ipc_2BOMe$) (1.19 g, 3.78 mmol) was dissolved in dry $Et_2O$ (1.0 M) and cooled to –78°C. Then allyl magnesium bromide (4.1 mL, 1.0 M solution in $Et_2O$, 4.1 mmol) was added dropwise and the mixture stirred for 15 min at –78°C and 1 hr at rt. The allylborane formed was cooled to –78°C and aldehyde **322** was added dropwise. The reaction mixture was stirred 2 hrs at –78°C and 1 hr at room temperature. Then the flask was cooled to 0°C and the mixture treated with 3 N NaOH and 30% aq. $H_2O_2$. The reaction was stirred at rt for 16 hrs. $Na_2S_2O_3$ was added, the organic layer separated, washed with $H_2O$ (×1) and brine (×2), dried over $MgSO_4$, filtered and evaporated. The crude was filtered through a short silica pad (ethyl acetate : petroleum ether = 1:9) in order to remove most of the Ipc-OH and submitted to the next step.

**(*2R,3R*)-3,5-dihydroxy-2-methylpentyl 2,4,6-triisopropylbenzoate (324a)**




To a solution of crude olefin **323a** in MeOH (7.0 mL) and $CH_2Cl_2$ (7.0 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (1.08 g, 28.5 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by flash column chromatography (ethyl acetate : petroleum ether = 4:6 ~ 8:2) to give diol **324a** (807 mg, 59% over 3 steps, 90:10 *dr*) as a colourless syrup.

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-H), 4.43 (dd, *J* = 11.0, 7.1 Hz, 1H, 5-$CH_a$), 4.18 (dd, *J* = 11.0, 6.2 Hz, 1H, 5-$H_b$), 3.99 (dt, *J* = 10.3, 3.0 Hz, 1H, 3-H), 3.89 (dt, *J* = 10.1, 4.8 Hz, 1H, 1-$H_a$), 3.81 (ddd, *J* = 10.8, 6.5, 2.5 Hz, 1H, 1-$H_b$), 2.95 – 2.76 (m, 3H, 3 × C*H*($CH_3$)$_2$), 2.66 (bs, 2H, OH) 1.97 (hd, *J* = 6.8, 3.3 Hz, 1H, 4-H), 1.82 (dtd, *J* = 14.2, 9.3, 4.3 Hz, 1H, 2-$H_a$), 1.61 (dddd, *J* = 14.5, 5.9, 3.8, 2.4 Hz, 1H, 2-$H_b$), 1.24 (d, *J* = 6.8 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.02 (d, *J* = 7.0 Hz, 3H, 6-H).

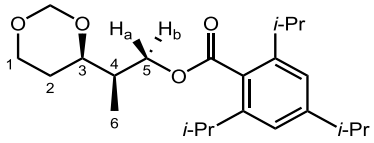
**$^{13}$C NMR** (100 MHz, Chloroform-d) δ 171.3 (C=O), 150.2 (C, Ar), 144.8 (2 × C, Ar), 130.3 (C, Ar), 120.9 (2 × CH, Ar), 72.2 (3-C), 67.4 (5-C), 62.2 (1-C), 38.4 (4-C), 35.6 (2-C), 34.4 (*C*H($CH_3$)$_2$), 31.6 (2 × *C*H($CH_3$)$_2$), 24.20 (CH(*C*$H_3$)$_2$), 24.18 (CH(*C*$H_3$)$_2$), 23.9 (CH(*C*$H_3$)$_2$), 11.0 (6-C).

**HRMS** (ESI) calc´d for $C_{22}H_{36}NaO_4$ $[M+Na]^+$ 387.2506; found: 387.2509.

$[\alpha]_D^{20}$ = –4.0 (*c* 1.0, $CHCl_3$)

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3405, 2961, 2871, 1724, 1462, 1250, 1069, 876.

**(*R*)-2-((*R*)-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (326)**




To a flask charged with the diol **324a** (400 mg, 1.11 mmol) were added *p*-toluenesulfonic acid (10 mg, 0.06 mmol) and 1,2-dimethoxymethane (2 mL). The reaction mixture was refluxed for 20 hrs. After the reaction mixture was concentrated under vacuo and purified by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 40:1) to give benzoate ester **326** (283 mg, 68%, 92:8 *dr*).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-H), 5.07 (d, *J* = 6.2 Hz, 1H, 7-$H_a$), 4.66 (d, *J* = 6.2 Hz, 1H, 7-$H_b$), 4.33 (dd, *J* = 11.0, 6.5 Hz, 1H, 5-$H_a$), 4.23 (dd, *J* = 11.0, 5.9 Hz, 1H, 5-$H_b$), 4.13 (ddt, *J* = 11.3, 4.9, 1.3 Hz, 1H, 1-$H_a$), 3.71 – 3.62 (m, 2H, 1-$H_a$ and 3-CH), 2.96 – 2.75 (m, 3H, 3 × C*H*($CH_3$)$_2$), 2.04 – 1.88 (m, 2H, 4-H and 2-$H_a$), 1.38 (ddt, *J* = 12.6, 2.6, 1.3 Hz, 1H, 2-$H_b$), 1.25 (d, *J* = 6.9 Hz, 12H, 2 × CH(C*H*$_3$)$_2$), 1.24 (d, *J* = 6.8 Hz, 6H, CH(C*H*$_3$)$_2$), 1.07 (d, *J* = 7.0 Hz, 3H, 6-H).

**$^{13}$C NMR** (100 MHz, Chloroform-d) δ 171.0 (C=O), 150.1 (C, Ar), 144.7 (2xC, Ar), 130.5 (C, Ar), 120.9 (2xCH, Ar), 94.0 (7-C), 76.9 (3-C), 66.7 (1-C), 66.4 (5-C), 37.4 (4-

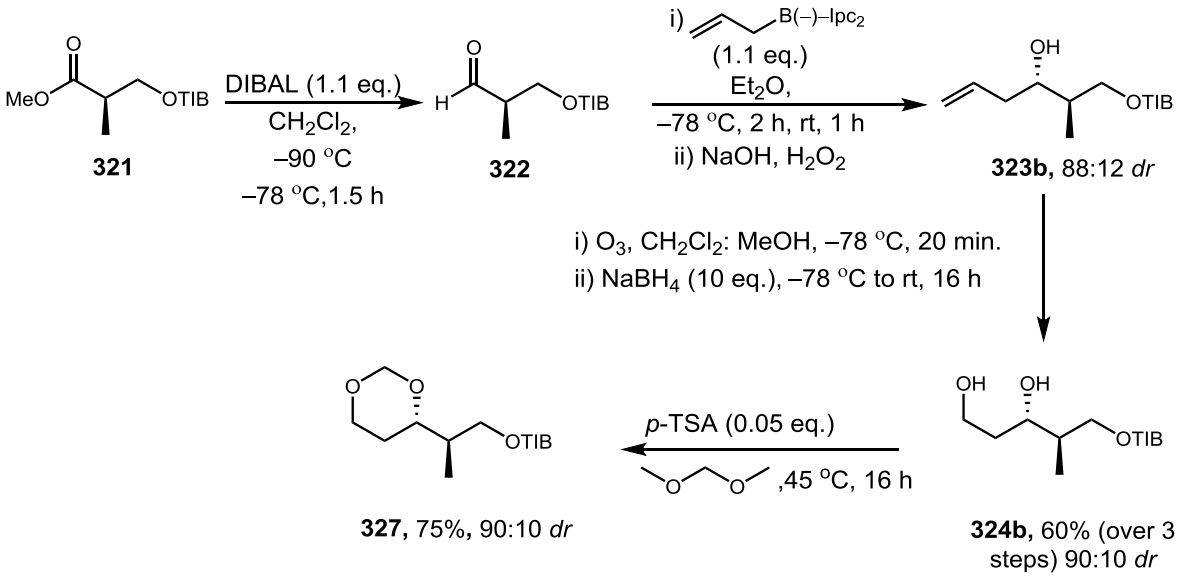
C), 34.4 (*C*H(CH$_3$)$_2$), 31.6 (2 × *C*H(CH$_3$)$_2$), 29.1 (2-C), 24.2 (2 × CH(*C*H$_3$)$_2$), 24.0 (CH(*C*H$_3$)$_2$), 11.9 (6-C).

**HRMS** (ESI) calc´d for $C_{23}H_{36}NaO_4$ $[M+Na]^+$ 399.2506; found: 399.2512.

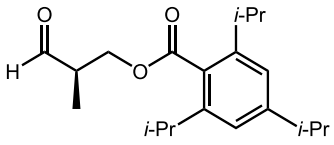
$[\alpha]_D^{20}$ = –5.0 (*c* 2.0, $CHCl_3$)

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2963, 2869, 1725, 1466, 1248, 1078, 1037, 990, 880.

**Synthesis of benzoate ester 327.**

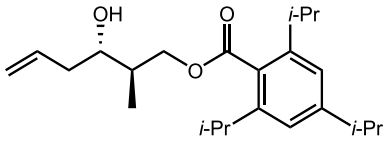



**(R)-2-methyl-3-oxopropyl 2,4,6-triisopropylbenzoate (322)**



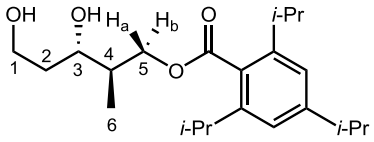

Ester **321** (1.60 g, 4.6 mmol) was stirred in $CH_2Cl_2$ (16 mL) and the solution was cooled to –90°C. DIBAL (1.0 M in hexanes, 5.0 mL, 5.0 mmol) was cooled to –90 °C and added dropwise. After addition of DIBAL the solution was transfer to cooling bath at –78°C and stirred for 90 min. Water (0.20 mL) was slowly added at –78°, followed by 15% NaOH solution (0.20 mL) and again water (0.50 mL). After warming up to room temperature the mixture was stirred for additional 30 min and $MgSO_4$ was added subsequently and the mixture stirred for another 30 min at rt. The precipitated salts were removed by filtration through celite using $Et_2O$ as eluent and solvent was removed under reduced pressure. Due to the instability of the aldehyde, the crude product was used in the next step without further purification.

**(*2R,3S*)-3-hydroxy-2-methylhex-5-en-1-yl 2,4,6-triisopropylbenzoate (323b)**




(–)-Diisopinocampheylmethoxyborane ($Ipc_2BOMe$) (1.76 g, 4.6 mmol) was dissolved in dry $Et_2O$ (1.0 M) and cooled to –78°C. Then allyl magnesium bromide (4.6 mL, 1.0 M solution in $Et_2O$, 4.6 mmol) was added dropwise and the mixture stirred for 15 min at –78°C and 1 hr at rt. The allylborane formed was cooled to –78°C and aldehyde **322** was added dropwise. The reaction mixture was stirred 2 hrs at –78°C and 1 hr at room temperature. Then the flask was cooled to 0°C and the mixture treated with 3 N NaOH and 30% aq. $H_2O_2$. The reaction was stirred at rt for 16 hrs. $Na_2S_2O_3$ was added, the organic layer separated, washed with $H_2O$ (×1) and brine (×2), dried over $MgSO_4$, filtered and evaporated. The crude was filtered through a short silica pad (ethyl acetate : petroleum ether = 1:9) in order to remove most of the Ipc-OH and submitted to the next step.

**(*2R,3S*)-3,5-dihydroxy-2-methylpentyl 2,4,6-triisopropylbenzoate (324b)**




To a solution of crude olefin **323b** in MeOH (9.5 mL) and $CH_2Cl_2$ (9.5 mL) was added some drops of Sudan-III indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition $NaBH_4$ (1.44 g, 38.1 mmol). The reaction was stirred for 1 hr at –78 °C, and then it was allowed to warm up to rt and stirred overnight. After that water was added, the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by flash column chromatography (ethyl acetate : petroleum ether = 4:6 ~ 8:2) to give diol **324b** (1.01 g, 60% over 3 steps, 90:10 *dr*) as a colourless syrup.

**$^{1}$H NMR** (400 MHz, Chloroform-d) 7.01 (s, 2H, Ar-H), 4.46 (dd, *J* = 10.9, 5.7 Hz, 1H, 5-$H_a$), 4.31 (dd, *J* = 10.9, 4.8 Hz, 1H, 5-$H_b$), 3.91 (ddd, *J* = 10.1, 5.7, 4.1 Hz, 1H, 1-$H_a$), 3.87–3.82 (m, 1H, 1-$H_b$), 3.79 (ddd, *J* = 9.8, 7.1, 3.3 Hz, 1H, 3-H), 2.94 – 2.78 (m, 3H, 3 × C*H*($CH_3$)$_2$), 2.75 (bs, 1H, OH), 2.02 – 1.93 (m, 1H, 4-CH), 1.86 – 1.65 (m, 2H, 2-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × C*H*($CH_3$)$_2$), 1.02 (d, *J* = 6.9 Hz, 3H, 6-H).

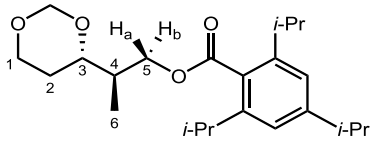
**$^{13}$C NMR** (100 MHz, Chloroform-d) 171.48 (C=O), 150.22 (C, Ar), 144.75 (2xC, Ar), 130.33 (C, Ar), 120.89 (2 × CH, Ar), 73.76 (3-C), 67.21 (5-C), 62.03 (1-C), 39.13 (4-C), 35.23 (2-C), 34.42 (*C*H($CH_3$)$_2$), 31.61 (2 × *C*H($CH_3$)$_2$), 24.21 (2 × CH(*C*$H_3$)$_2$), 23.94 (CH(*C*$H_3$)$_2$), 13.74 (6-C).

**HRMS** (ESI) calc´d for $C_{22}H_{36}NaO_4$ $[M+Na]^+$ 387.2506; found: 387.2498.

$[\alpha]_D^{20}$ = +1.0 (*c* 1.0, $CHCl_3$)

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3413, 2961, 2871, 1723, 1461, 1250, 1068, 876, 876.

**(*R*)-2-((*S*)-1,3-dioxan-4-yl)propyl 2,4,6-triisopropylbenzoate (327)**




To a flask charged with the diol **324b** (400 mg, 1.11 mmol) were added *p*-toluenesulfonic acid (10 mg, 0.06 mmol) and 1,2-dimethoxymethane (2 mL). The reaction mixture was refluxed for 20 hrs. After the reaction mixture was concentrated under vacuo and purified by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 40:1) to give benzoate ester **327** (311 mg, 75%, 90:10 *dr*).

**$^{1}$H NMR** (400 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-H), 5.07 (d, *J* = 6.2 Hz, 1H, 7-$H_a$), 4.65 (d, *J* = 6.2 Hz, 1H, 7-$H_b$), 4.36 (dd, *J* = 11.0, 4.5 Hz, 1H, 5-$H_a$), 4.30 (dd, *J* = 11.0, 5.6 Hz, 1H, 5-$H_b$), 4.14 (ddt, *J* = 11.4, 4.9, 1.4 Hz, 1H, 1-$H_a$), 3.67 (td, *J* = 11.9, 2.5 Hz, 1H, 1-$H_b$), 3.54 (ddd, *J* = 10.9, 7.9, 2.4 Hz, 1H, 3-H), 2.97 – 2.77 (m, 3H, 3 × C*H*($CH_3$)$_2$), 2.09 – 1.98 (m, 1H, 4-H), 1.86 – 1.73 (dtd, *J* = 12.8, 11.3, 4.8 Hz, 1H, 2-$H_a$), 1.52 (ddt, *J* = 12.8, 4.3, 2.3 Hz, 2-$H_b$), 1.27 – 1.23 (m, 18H, 3 × CH(C*H*$_3$)$_2$), 1.00 (d, *J* = 7.1 Hz, 1H, 6-H).

**$^{13}$C NMR** (100 MHz, Chloroform-d) δ 171.1 (C=O), 150.1 (C, Ar), 144.7 (2xC, Ar), 130.7 (C, Ar), 120.9 (2 × CH, Ar), 93.9 (7-C), 77.3 (3-CH), 66.6 (1-C), 66.1 (7-C), 37.6

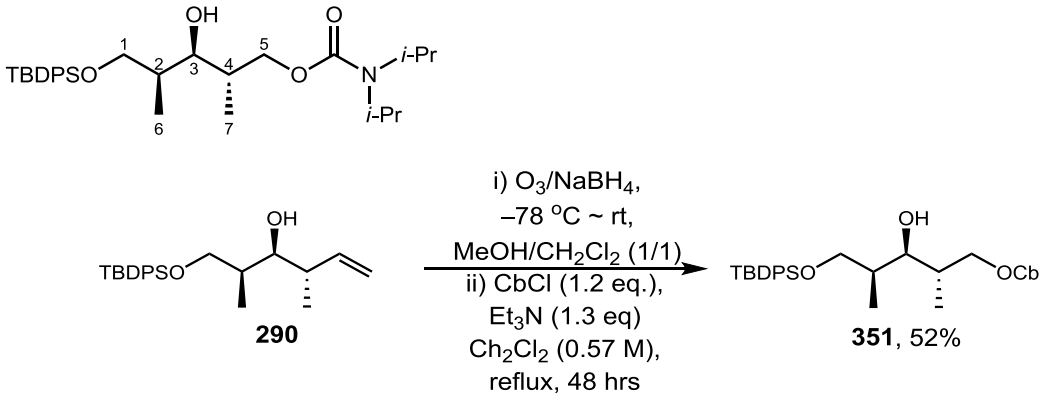
(4-C), 34.4 (*C*H(CH$_3$)$_2$), 31.5 (2 × *C*H(CH$_3$)$_2$), 29.3 (2-C), 24.2 (2 × CH(*C*H$_3$)$_2$), 24.0 (CH(*C*H$_3$)$_2$), 12.7 (6-C).

**HRMS** (ESI) calc´d for $C_{23}H_{36}NaO_4$ $[M+Na]^+$ 399.2506; found: 399.2521.

$[\alpha]_D^{20}$ = +6.5 (*c* 2.0, $CHCl_3$)

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2961, 2875, 1723, 1462, 1248, 1040, 988, 876, 755.

**(*2S,3S,4S*)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,4-dimethylpentyl diisopropylcarbamate (351)**




To a solution of compound **279** (937 mg, 2.45 mmol) in MeOH (6.1 mL) and $CH_2Cl_2$ (6.1 mL) was added some drops of Sudan-III solution indicator (light pink solution). Then $O_3$ was passed through the solution at –78 °C until the solution became colourless. Subsequently, the mixture was purged with $N_2$ for 15 min, followed by addition of $NaBH_4$ (927 mg, 24.5 mmol). The reaction was stirred for 1 hr at –78 °C, then it was allowed to warm up to rt and stirred overnight. After that water was added, and the reaction mixture was concentrated under vacuo until 1/4 of the original volume. Then water was added again, and the mixture was extracted with ethyl acetate (×3). The organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude oil was subjected to next step without further purification.

A solution of crude alcohol from last step, diisopropyl carbamoyl chloride (CbCl) (483 mg, 1.6 mmol) and $Et_3N$ (0.44 mL, 322 mg, 3.2 mmol) in anhydrous $CH_2Cl_2$ (4.5 mL) was heated under reflux for 48 hrs. Then, the reaction mixture was poured in water and extracted with diethyl ether (×3). The combined organic phases were washed with water, brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was

purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:50 ~ 1:20) to afford pure carbamate **280** (660 mg, 52%).

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.70 – 7.64 (m, 4H, Ar-CH), 7.46 – 7.35 (m, 6H, Ar-CH), 4.52 (dd, *J* = 11.0, 4.5 Hz, 1H, 5-H), 4.08 (dd, *J* = 11.0, 3.1 Hz, 1H, 5-H), 3.74 (dd, *J* = 9.9, 6.9 Hz, 1H, 1-H), 3.67 (dd, *J* = 9.9, 4.6 Hz, 1H, 1-H), 3.47 (dd, *J* = 11.2, 5.3 Hz, 1H, 3-H), 1.92 – 1.78 (m, 2H, 2-H + 4-H), 1.20 (d, *J* = 6.9 Hz, 12H, 2 × CH(C*H*$_3$)$_2$), 1.05 (s, 9H, C(CH$_3$)$_3$), 0.95 (d, *J* = 6.9 Hz, 3H, CH$_3$), 0.87 (d, *J* = 7.0 Hz, 3H, CH$_3$).

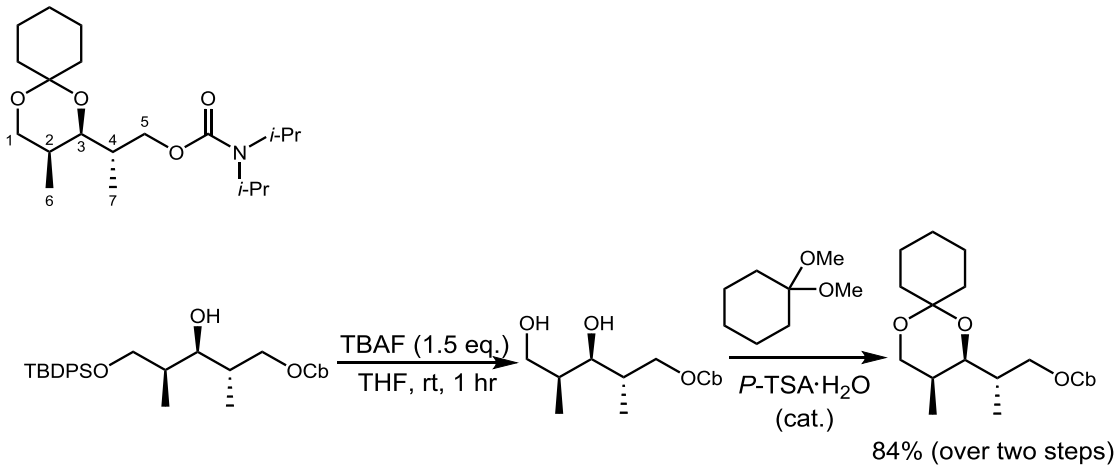
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 155.0 (C=O), 135.8 (Ar-CH), 133.9 (Ar-C), 129.7 (Ar-C), 127.7 (Ar-CH), 75.8 (O-C), 66.7 (O-C), 66.4 (O-C), 66.0 (N-C), 35.9 (CH), 35.5 (CH), 27.0 (C(*C*H$_3$)$_3$), 19.4 (*C*(CH$_3$)$_3$), 14.3 (CH$_3$), 12.1 (CH$_3$).

**HRMS (ESI)** calc'd for $C_{30}H_{47}NO_4SiNa$ [M+Na]+: 536.3172; found: 536.3175.

$[\alpha]_D^{20}$ = +4.2 (c 1.2, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2966, 2931, 2860, 1668, 1473, 1429, 1302, 1112, 1057, 702, 505, 423.

**(*S*)-2-((*2R,3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)propyl diisopropylcarbamate (345)**




**351** **352** **345**

A solution of TBAF (1.9 mL, 1.0 M in THF, 1.9 mmol) was added dropwise to a solution of carbamate **351** (638 mg, 1.24 mmol) in anhydrous THF (12.4 mL). The colourless mixture was then stirred at rt for 1 hr. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were separated, and the aqueous phase

was extracted with diethyl ether (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtrated over a short silica pad (ethyl acetate : petroleum ether = 1:9) to afford the crude diol as colourless oil without further purification.

To a solution of the crude diol from last step in 1,1-dimethoxycyclohexane (1.7 mL, 11.4 mmol) was added *p*-toluenesulfonic acid monohydrate (10.9 mg, 0.057 mmol). The reaction was stirred for 12 hrs at rt. After that the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (×3). The combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum and purified through flash chromatography (ethyl acetate : petroleum ether = 1:30) on silica gel to afford carbamate **345** (372 mg, 84%).

**$R_f$**: 0.12 (ethyl acetate/petroleum ether: 0.05)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 4.21 (dd, *J* = 10.4, 3.1 Hz, 1H, 5-H), 4.16 – 4.12 (m, 2H, 1-H+5-H), 3.72 (dd, *J* = 10.4, 2.3 Hz, 1H, 3-H), 3.58 (dd, *J* = 11.5, 1.6 Hz, 1H, 1-H), 2.23 – 2.07 (m, 2H, $CH_2$), 1.95 – 1.81 (m, 1H, CH), 1.71 – 1.30 (m, 9H, CH + 4 × $CH_2$), 1.20 (d, *J* = 6.7 Hz, 12H, 2 × CH(C*H*$_3$)$_2$), 1.07 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.91 (d, *J* = 6.9 Hz, 3H, $CH_3$)).

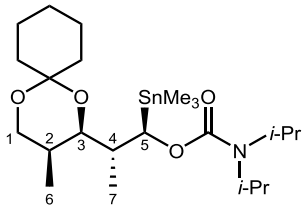
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 156.0 (C=O), 98.8 (O-C-O), 71.5 (3-C), 66.6 (5-C), 66.5 (1-C), 38.7 (Cy-$CH_2$), 35.0 (CH), 29.9 (CH), 27.7 (Cy-$CH_2$), 25.9 (Cy-$CH_2$), 22.8 (Cy-$CH_2$), 22.7 (Cy-$CH_2$), 12.7 ($CH_3$), 10.6 ($CH_3$).

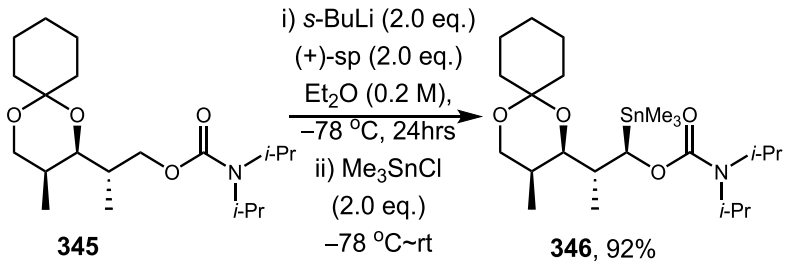
**HRMS (ESI)** calc'd for $C_{20}H_{37}NO_4Na$ [M+Na]+: 378.2620; found: 378.2622.

$[\alpha]_D^{20}$ = –21.5 (c 0.79, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2933, 1685, 1438, 1367, 1288, 1133, 1116, 1052, 770.

**(*1R,2R*)-2-((*2R,3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)-1-(trimethylstannyl)propyl diisopropylcarbamate (346)**






To a solution of carbamate **345** (107 mg, 0.30 mmol) and (+)-sparteine (141 mg, 0.60 mmol) in dry $Et_2O$ (1.5 mL) at –78 °C was added *s*-BuLi (0.46 mL, 0.60 mmol, 1.3 M in cyclohexane/hexane=92:8) dropwise. This mixture was stirred at –78 °C for 24 hrs. A solution of $Me_3SnCl$ (0.6 mL, 0.60 mmol, 1.0 M in hexane) was added dropwise over and the reaction was stirred for 3 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at rt. The reaction mixture was oxidized with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at room temperature. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum = 1:30) to afford stannane **346** (142.7 mg, 92%).

**$R_f$**: 0.19 (ethyl acetate : petroleum = 1:20)

**$^1$H NMR** (500 MHz, Chloroform-d) δ 4.95 (d, *J* = 1.5 Hz, 1H, 5-H), 4.15 (dd, *J* = 11.4, 2.8 Hz, 1H, 1-H), 3.90 (dd, *J* = 9.9, 2.3 Hz, 1H, 3-H), 3.60 (dd, *J* = 11.4, 1.5 Hz, 1H, 1-H), 2.23 – 2.08 (m, 1H, CH), 1.92 – 1.81 (m, 1H, CH), 1.76 – 1.33 (m, 10H, Cy-$CH_2$), 1.20 (d, , *J* = 6.9 Hz, 12H, CH($CH_3$)$_2$), 1.07 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.97 (d, *J* = 7.0 Hz, 3H, $CH_3$), 0.11 (s, 9H, 3 × Sn- $CH_3$).

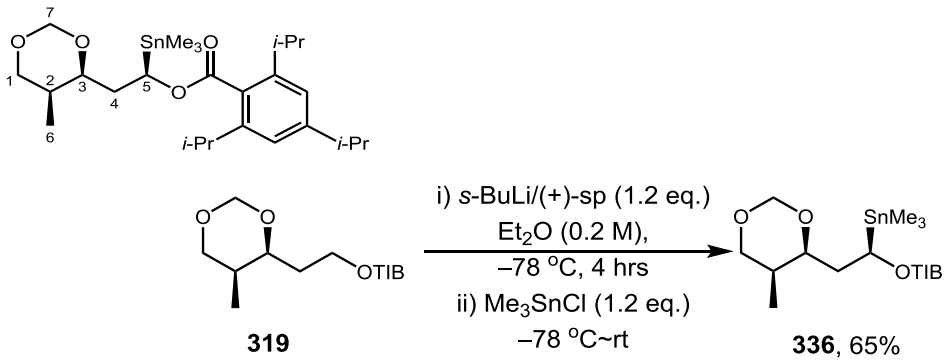
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 155.7 (C=O), 99.1 (O-C-O), 73.0 (5-C), 71.1 (3-C), 66.7 (1-C), 38.8 (Cy-$CH_2$), 38.4 (CH), 30.3 (CH), 27.7 (Cy-$CH_2$), 26.0 (Cy-$CH_2$), 22.9 (Cy-$CH_2$), 22.7 (Cy-$CH_2$), 13.5 ($CH_3$), 10.5 ($CH_3$), –7.9 (Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{23}H_{45}NO_4SnNa$ [M+Na]+: 542.2268; found: 542.2270.

$[\alpha]_D^{20}$ = –66.3 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2960, 1687, 1461, 1364, 1275, 1131, 1111, 1044, 967, 503.

**(*R*)-2-((*4S,5S*)-5-methyl-1,3-dioxan-4-yl)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (336)**




To a solution of benzoate ester **319** (30 mg, 0.08 mmol) and (+)-sparteine (37 mg, 0.16 mmol) in dry $Et_2O$ (0.4 mL) at –78 °C was added *s*-BuLi (0.12 mL, 0.16 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 4 hrs. A solution of $Me_3SnCl$ (0.16 mL, 0.16 mmol, 1.0 M in hexane) was added dropwise and the reaction was stirred for 4 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at room temperature. The reaction mixture was oxidised with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum ether = 1:30) to afford compound **336** (28 mg, 65%, 96:4 *d.r.*) with benzoate ester **319** (6 mg, 20%) recovered.

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.01 (s, 2H, Ar-CH), 5.08 (dd, *J* = 5.4, 4.5 Hz, 1H, 5-H), 5.04 (d, *J* = 6.1 Hz, 1H, 7-H), 4.64 (d, *J* = 6.1 Hz, 1H, 7-H), 3.88 – 3.83 (m, 2H, 1-H), 3.78 (dd, *J* = 11.2, 2.6 Hz, 1H, 3-H), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.05 – 1.87 (m, 2H, 4-H), 1.52 – 1.40 (m, 1H, 2-H), 1.25 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.14 (d, *J* = 7.0 Hz, 1H, $CH_3$), 0.20 (s, 9H, 3 × Sn-$CH_3$).

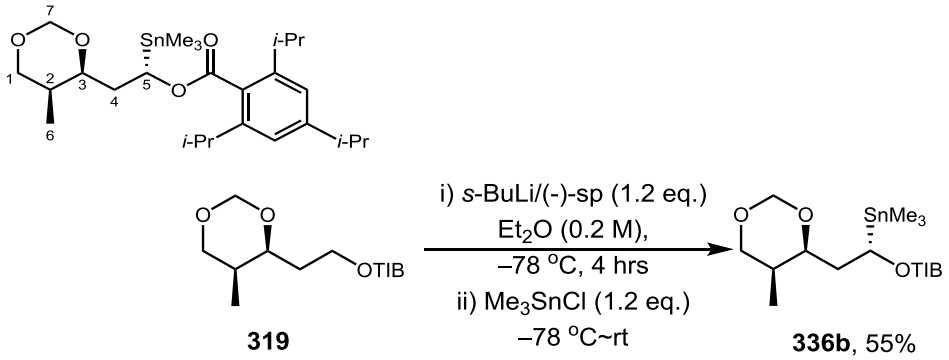
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.4 (C=O), 150.2 (Ar-C), 144.9 (Ar-C), 130.8 (Ar-C), 121.0 (Ar-CH), 94.4 (7-C), 75.9 (3-C), 73.5 (5-C), 68.0 (1-C), 37.1 (CH), 34.5 (*C*H$(CH_3)_2$), 33.4 ($CH_2$), 31.6 (2 × *C*H$(CH_3)_2$), 24.6 (CH(*C*$H_3)_2$), 24.4 (CH(*C*$H_3)_2$), 24.1 (CH(*C*$H_3)_2$), 11.3 (6-$CH_3$), -8.9 (Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{26}H_{44}O_4SnNa$ [M+Na]+: 563.2159; found: 563.2161.

$[\alpha]_D^{20}$ = –15 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2957, 2860, 1716, 1607, 1460, 1375, 1259, 1070, 958, 753.

**(*S*)-2-((*4S,5S*)-5-methyl-1,3-dioxan-4-yl)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (336b)**




**319** **336b**, 55%

To a solution of benzoate ester **319** (30 mg, 0.08 mmol) and (–)-sparteine (37 mg, 0.16 mmol) in dry $Et_2O$ (0.4 mL) at –78 °C was added *s*-BuLi (0.12 mL, 0.16 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 4 hrs. A solution of $Me_3SnCl$ (0.16 mL, 0.16 mmol, 1.0 M in hexane) was added dropwise and the reaction was stirred for 4 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at room temperature. The reaction mixture was oxidised with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum ether = 1:100) to afford compound **336b** (23.7 mg, 55%, 97:3 *d.r.*) with benzoate ester **319** (10.5 mg, 35%) recovered.

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 5.17 (t, *J* = 5.4 Hz, 1H, 5-H), 4.98 (d, *J* = 6.0 Hz, 1H, 7-H ), 4.59 (d, *J* = 6.0 Hz, 1H, 7-H), 3.94 – 3.83 (m, 2H, 1-H), 3.77 (dd, *J* = 11.1, 2.3 Hz, 1H, 3-H), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.15 – 1.96 (m, 2H, 4-H), 1.54 – 1.46 (m, 1H, 2-H), 1.24 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.13 (d, *J* = 7.0 Hz, 3H, $CH_3$), 0.17 (s, 9H, 3 × Sn-$CH_3$).

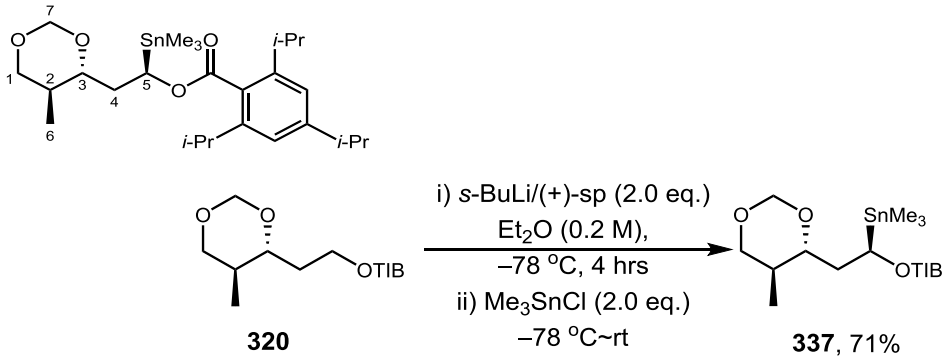
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.4 (C=O), 150.2 (Ar-C), 144.8 (Ar-C), 130.9 (Ar-C), 121.0 (Ar-CH), 94.3 (7-C), 75.9 (3-C), 73.6 (5-C), 67.7 (1-C), 36.8 (CH), 34.5 (*C*H(CH$_3$)$_2$), 32.5 (CH$_2$), 31.7 (2 × *C*H(CH$_3$)$_2$), 24.6 (CH(*C*H$_3$)$_2$), 24.4 (CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 11.2 (6-CH$_3$), –8.25 (Sn-CH$_3$).

**HRMS (ESI)** calc'd for $C_{26}H_{44}O_4SnNa$ [M+Na]+: 563.2159; found: 563.2158.

$[\alpha]_D^{20}$ = –7 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2958, 2859, 1719, 1609, 1458, 1375, 1255, 1070, 956, 752.

**(*R*)-2-((*4R,5S*)-5-methyl-1,3-dioxan-4-yl)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (337)**




To a solution of benzoate ester **20** (30 mg, 0.08 mmol) and (+)-sparteine (37 mg, 0.16 mmol) in dry $Et_2O$ (0.4 mL) at –78 °C was added *s*-BuLi (0.12 mL, 0.16 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 4 hrs. A solution of $Me_3SnCl$ (0.16 mL, 0.16 mmol, 1.0 M in hexane) was added dropwise and the reaction was stirred for 4 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at room temperature. The reaction mixture was oxidised with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum ether = 1:100) to afford compound **337** (30.5 mg, 71%, 96:4 *d.r.*) with benzoate ester **320** (3 mg, 10%) recovered.

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 5.33 (dd, *J* = 6.7, 3.3 Hz, 1H, 5-H), 5.01 (d, *J* = 6.1 Hz, 1H, 7-H), 4.55 (d, *J* = 6.1 Hz, 1H, 7-H), 3.95 (dd, *J* = 11.4, 4.6 Hz, 1H, 1-H), 3.35 (t, *J* = 9.2 Hz, 1H, 3-H), 3.19 (dd, *J* = 11.4, 11.2 Hz, 1H, 1-H), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.51 (ddd, *J* = 14.6, 6.6, 2.1 Hz, 1H, 4-H), 1.97 – 1.86 (m, 1H, 4-H), 1.81 (m, 1H, 2-H), 1.23 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$ ), 0.73 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.14 (s, 9H, 3 × Sn-$CH_3$).

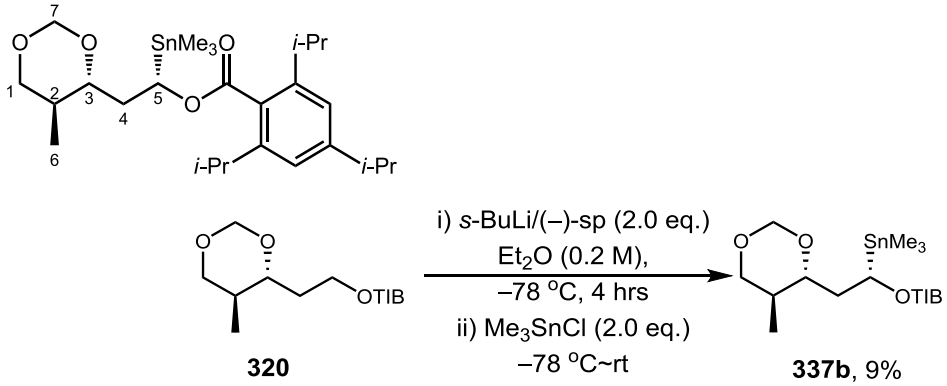
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 171.4 (C=O), 150.0 (Ar-C), 144.9 (Ar-C), 131.0 (Ar-C), 121.0 (Ar-CH), 93.6 (7-C), 79.6 (3-C), 72.7 (5-C), 67.8 (1-C), 36.6 (CH), 35.1 (*C*H($CH_3$)$_2$), 34.5 ($CH_2$), 31.6 (2 × *C*H($CH_3$)$_2$), 24.7 (CH(*C*$H_3$)$_2$), 24.4 (CH(*C*$H_3$)$_2$), 24.1 (CH(*C*$H_3$)$_2$), 12.6 ($CH_3$), –7.8 (Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{26}H_{44}O_4SnNa$ [M+Na]+: 563.2159; found: 563.2156.

$[\alpha]_D^{20}$ = –4 (c 1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2961, 2859, 1721, 1605, 1572, 1460, 1361, 1283, 1245, 1076, 1028, 956, 757.

**(*S*)-2-((*4R,5S*)-5-methyl-1,3-dioxan-4-yl)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (337b)**




**320** **337b**, 9%

To a solution of benzoate ester **20** (30 mg, 0.08 mmol) and (–)-sparteine (37 mg, 0.16 mmol) in dry $Et_2O$ (0.4 mL) at –78 °C was added *s*-BuLi (0.12 mL, 0.16 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 4 hrs. A solution of $Me_3SnCl$ (0.16 mL, 0.16 mmol, 1.0 M in hexane) was added dropwise and the reaction was stirred for 4 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at room temperature. The reaction mixture was oxidised with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was

washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum ether = 1:100) to afford compound **337b** (4 mg, 9%, > 95:5 *d.r.*) with benzoate ester **320** (18 mg, 60%) recovered.

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 5.18 (dd, *J* = 11.3, 3.4 Hz, 1H, 5-H), 5.07 (d, *J* = 6.2 Hz, 1H, 7-H), 4.59 (d, *J* = 6.2 Hz, 1H, 7-H), 3.95 (dd, *J* = 11.3, 4.7 Hz, 1H, 1-H), 3.34 (t, *J* = 9.2 Hz, 1H, 3-H), 3.20 (dd, *J* = 11.3, 11.2 Hz, 1H, 1-H), 2.86 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*($CH_3$)$_2$), 2.43 – 2.24 (m, 1H, 2-H), 1.88 – 1.68 (m, 2H, 4-H), 1.24 (d, *J* = 6.90 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 0.72 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.19 (s, 9H, 3 × Sn-$CH_3$).

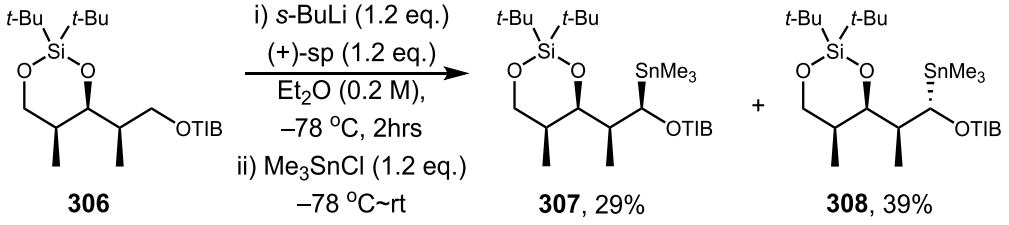
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.4 (C=O), 150.1 (Ar-C), 145.0 (Ar-C), 130.8 (Ar-C), 121.0 (Ar-CH), 93.9 (7-C), 79.4 (3-C), 72.7 (5-C), 67.3 (1-C), 36.8 (CH), 35.2 (*C*H($CH_3$)$_2$), 34.5 ($CH_2$), 31.6 (2 × *C*H($CH_3$)$_2$), 24.63 (CH(*C*$H_3$)$_2$), 24.4 (CH(*C*$H_3$)$_2$), 24.1 (CH(*C*$H_3$)$_2$), 12.7 ($CH_3$), –8.8 (Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{26}H_{44}O_4SnNa$ [M+Na]+: 563.2159; found: 563.2162.

$[\alpha]_D^{20}$ = –6 (c 0.2, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2957, 2867, 1720, 1604, 1571, 1459, 1281, 1239, 1074, 1027, 954, 752.

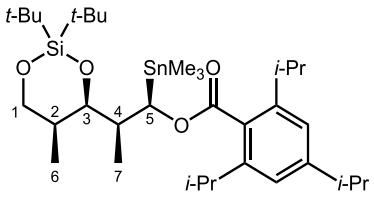
**Synthesis of stannanes 307 and 308 from benzoate ester 306**




To a solution of benzoate ester **307** (100 mg, 0.19 mmol) and (+)-sparteine (54.2 mg, 0.23 mmol) in dry $Et_2O$ (1.0 mL) at –78 °C was added *s*-BuLi (0.18 mL, 0.23 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 2 hrs. A solution of $Me_3SnCl$ (0.23 mL, 0.23 mmol, 1.0 M in hexane) was added dropwise over 20 min and the reaction was stirred for 3 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further

20 min at rt. The reaction mixture was oxidized with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum = 1:100) to afford stannanes **307** (38.5 mg, 29%) and **308** (38.5 mg, 39%) starting material (32 mg, 32%) recovered.

**(*1R,2S*)-2-((*4R,5S)*-2,2-di-tert-butyl-5-methyl-1,3,2-dioxasilinan-4-yl)-1-(trimethylstannyl)propyl 2,4,6-triisopropylbenzoate (307)**




**$R_f$**: 0.26 (ethyl acetate : petroleum = 1:50)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 5.00 (s, 1H, 5-H), 4.35 (dd, *J* = 11.2, 2.5 Hz, 1H, 1-H), 4.19 (dd, *J* = 9.5, 2.3 Hz, 1H, 3-H), 3.92 (dd, *J* = 11.2, 1.5 Hz, 1H, 1-H), 2.81 (hept, *J* = 6.9 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.02 – 1.86 (m, 2H, 2-H + 4-H), 1.23 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3)_2$), 1.20 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.14 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.04 (dd, *J* = 6.3, 2.7 Hz, 18H, 2 × C$(CH_3)_3$), 0.25 (s, 9H, 3 × Sn-$CH_3$).

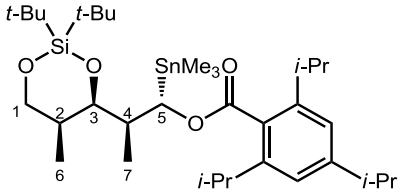
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.8 (C=O), 150.1 (Ar-CH), 144.9 (Ar-C), 130.6 (Ar-C), 121.0 (Ar-CH), 78.4 (O-C), 73.6 (O-C), 71.4 (O-C), 41.2 (CH), 34.5 (*C*H$(CH_3)_2$), 31.8 (2 × *C*H$(CH_3)_2$), 28.9 (CH), 27.8 (*C*$(CH_3)_3$), 24.6 (CH(*C*H$_3)_2$), 24.5 (CH(*C*H$_3)_2$), 24.1 (CH(*C*H$_3)_2$), 23.6 (C(*C*H$_3)_3$), 20.8 (C(*C*H$_3)_3$), 14.3 ($CH_3$), 11.3 ($CH_3$), –7.7 (3 × Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{34}H_{62}O_4SiSnNa$ [M+Na]+: 705.3337; found: 705.3339.

$[\alpha]_D^{20}$ = +7 (c 0.4, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2963, 2931, 2857, 1711, 1607, 1463, 1250, 1101, 996, 769, 443.

**(*1S*,*2S*)-2-((*4R*,*5S*)-2,2-di-tert-butyl-5-methyl-1,3,2-dioxasilinan-4-yl)-1-(trimethylstannyl)propyl 2,4,6-triisopropylbenzoate (308)**




**R$_f$**: 0.18 (ethyl acetate : petroleum = 1:50)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.00 (s, 2H, Ar-CH), 5.35 (d, *J* = 3.9 Hz, 1H, 5-H), 4.35 (dd, *J* = 11.3, 2.5 Hz, 1H, 1-H), 4.03 (dd, *J* = 9.5, 2.2 Hz, 1H, 3-H), 3.94 (dd, *J* = 11.3, 1.2 Hz, 1H), 2.85 (hept, *J* = 6.9 Hz, 3H, 3 × CH(C*H*$_3$)$_2$), 2.39 – 2.23 (m, 1H), CH, 1.79 – 1.64 (m, 1H, CH), 1.30 (d, *J* = 7.2 Hz, 3H, CH$_3$), 1.24 (d, *J* = 6.9 Hz, 18H, 3 × CH(C*H*$_3$)$_2$), 1.17 (d, *J* = 7.2 Hz, 3H, CH$_3$), 1.09 (s, 9H, C(CH$_3$)$_3$), 1.05 (s, 9H, C(CH$_3$)$_3$), 0.23 (s, 9H, 3 × Sn-CH$_3$).

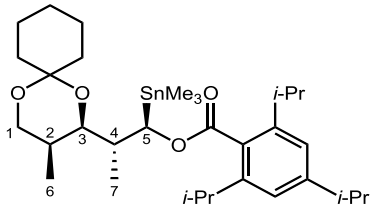
$^{13}$C NMR (101 MHz, Chloroform-d) δ 171.4 (C=O), 150.0 (Ar-C), 145.0 (Ar-C), 130.8 (Ar-C), 121.0 (Ar-CH), 77.6 (O-C), 74.3 (O-C), 71.3 (O-C), 43.1 (CH), 35.8 (*C*(CH$_3$)$_3$), 34.5 (*C*H(CH$_3$)$_2$), 31.6 (2 × *C*H(CH$_3$)$_2$), 28.9 (CH), 27.7 (*C*(CH$_3$)$_3$), 24.7 (CH(*C*H$_3$)$_2$), 24.3 (CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 23.7 (C(*C*H$_3$)$_3$), 20.8 (C(*C*H$_3$)$_3$), 16.4 (CH$_3$), 10.9 (CH$_3$), –7.5 (3 × Sn-CH$_3$).

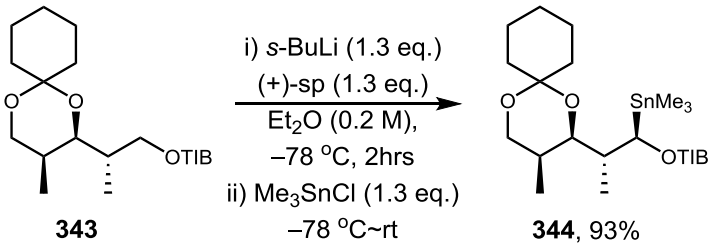
**HRMS (ESI)** calc'd for $C_{34}H_{62}O_4SiSnNa$ [M+Na]+: 705.3337; found: 705.3335.

$[\alpha]_D^{20}$ = –5.98 (c 0.84, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2962, 2940, 2863, 1716, 1607, 1462, 1364, 1248, 1104, 996, 826, 768, 526, 444.

**(*1R*,*2R*)-2-((*2R*,*3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)-1-(trimethylstannyl)propyl 2,4,6-triisopropylbenzoate (344)**






**343** **344**, 93%

To a solution of benzoate ester **343** (69 mg, 0.15 mmol) and (+)-sparteine (45.7 mg, 0.20 mmol) in dry $Et_2O$ (0.75 mL) at –78 °C was added *s*-BuLi (0.15 mL, 0.20 mmol, 1.3 M in cyclohexane/hexane=92:8) dropwise. This mixture was stirred at –78 °C for 2 hrs. A solution of $Me_3SnCl$ (0.23 mL, 0.23 mmol, 1.0 M in hexane) was added dropwise over 20 min and the reaction was stirred for 3 hrs at –78 °C. After that 5% $H_3PO_4$ aqueous solution was added at –78 °C and the reaction mixture was stirred for further 20 min at rt. The reaction mixture was oxidized with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was separated, and the organic layer was washed with 5% $H_3PO_4$ aqueous solution 3 times. The combined aqueous layers were extracted with $Et_2O$ 3 times. Then the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography (ethyl acetate : petroleum = 1:20) to afford stannane **344** (87 mg, 93%).

**Rf**: 0.81 (ethyl acetate : petroleum = 1:20)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 6.99 (d, *J* = 10.4 Hz, 2H, Ar-CH), 5.27 (s, 1H, 5-H), 4.04 (dd, *J* = 11.4, 2.3 Hz, 1H, 1-H), 3.85 (dd, *J* = 9.7, 2.1 Hz, 1H, 3-H), 3.58 (dd, *J* = 11.4, 1.1 Hz, 1H, 1-H), 2.86 (hept, *J* = 6.8 Hz, 3H, 3 × C*H*$(CH_3)_2$), 2.03 – 1.72 (m, 2H, 2-H + 4-H), 1.25 (d, *J* = 6.8 Hz, 21H, 3 × CH(C*H*$_3)_2$ + 3 × $CH_3$), 1.07 (d, *J* = 7.3 Hz, 3H, $CH_3$), 0.23 (s, 9H, 3 × Sn-$CH_3$).

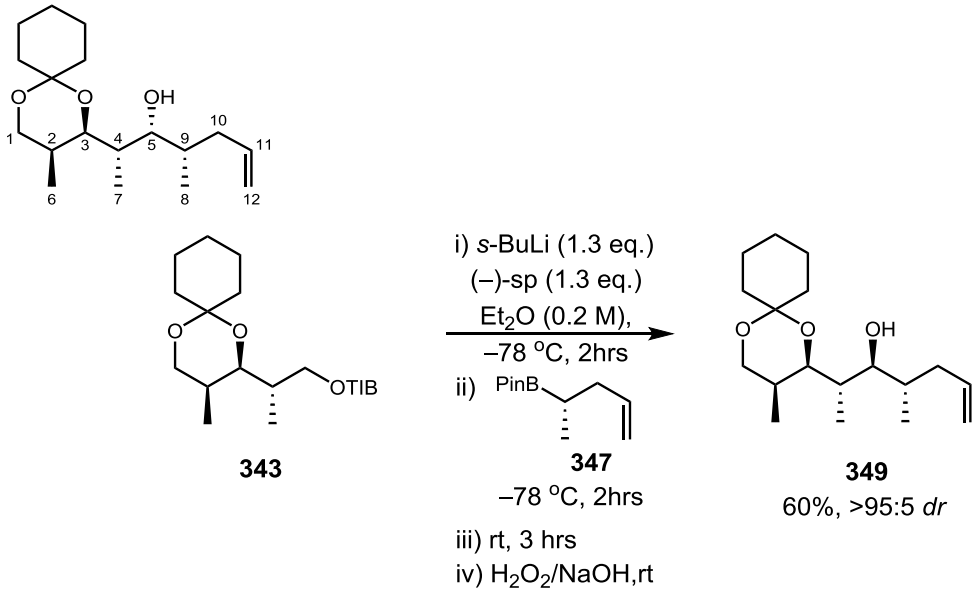
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 171.3 (C=O), 149.9 (Ar-C), 145.1 (Ar-C), 130.5 (Ar-C), 120.9 (Ar-CH), 98.8 (O-C-O), 73.1 (O-C), 70.6 (O-C), 66.4 (O-C), 38.7 (Cy-$CH_2$ + CH), 34.3 (*C*H$(CH_3)_2$), 31.6 (2 × *C*H$(CH_3)_2$), 30.2 (CH), 27.9 (Cy-$CH_2$), 25.8 (Cy-$CH_2$), 24.5 (2 × CH(*C*H$_3)_2$), 23.9 (CH(*C*H$_3)_2$), 22.7 (Cy-$CH_2$), 22.5 (Cy-$CH_2$), 12.1 ($CH_3$), 10.1 ($CH_3$), –7.8 (3 × Sn-$CH_3$).

**HRMS (ESI)** calc'd for $C_{32}H_{54}NaO_4Sn$ [M+Na]+: 645.2942; found: 645.2945.

$[\alpha]_D^{20}$ = –37.5 (c 0.4, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2961, 2931, 2866, 1698, 1463, 1286, 1253, 1077, 999, 962, 765, 524.

**(*2S,3R,4S*)-4-methyl-2-((*2R,3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)hept-6-en-3-ol (349)**




To a solution of benzoate ester **343** (80 mg, 0.17 mmol) and (+)-sparteine (53.1 mg, 0.23 mmol) in dry $Et_2O$ (0.85 mL) at –78 °C was added *s*-BuLi (0.17 mL, 0.23 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 2 hrs. A solution of boronic ester **347** (45 mg, 0.23 mmol, 0.5 M in $Et_2O$) was added dropwise and the reaction was stirred for 3 hrs min at –78 °C. The reaction was then warmed to rt and stirred for 3 hrs. The reaction mixture was oxidized with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at room temperature. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:20) to afford compound **349** (30.5 mg, 60%).

**$R_f$**: 0.48 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.76 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H, 11-H), 5.11 – 4.95 (m, 2H, 12-H), 4.13 (dd, *J* = 11.4, 2.4 Hz, 1H, 1-H), 3.91 (dd, *J* = 9.7, 2.1 Hz, 1H, OCH), 3.70 (d, *J* = 8.5 Hz, 1H, OCH), 3.58 (dd, *J* = 11.4, 1.2 Hz, 1H, 1-H), 2.23 –

2.00 (m, 2H, Cy-$CH_2$), 1.96 – 1.10 (m, 13H, 4 × Cy-$CH_2$ + 10-$CH_2$ + 3 × CH), 1.06 (d, *J* = 6.9 Hz, 3H, $CH_3$), 1.00 (d, *J* = 6.6 Hz, 3H, $CH_3$), 0.76 (d, *J* = 7.0 Hz, 3H, $CH_3$).

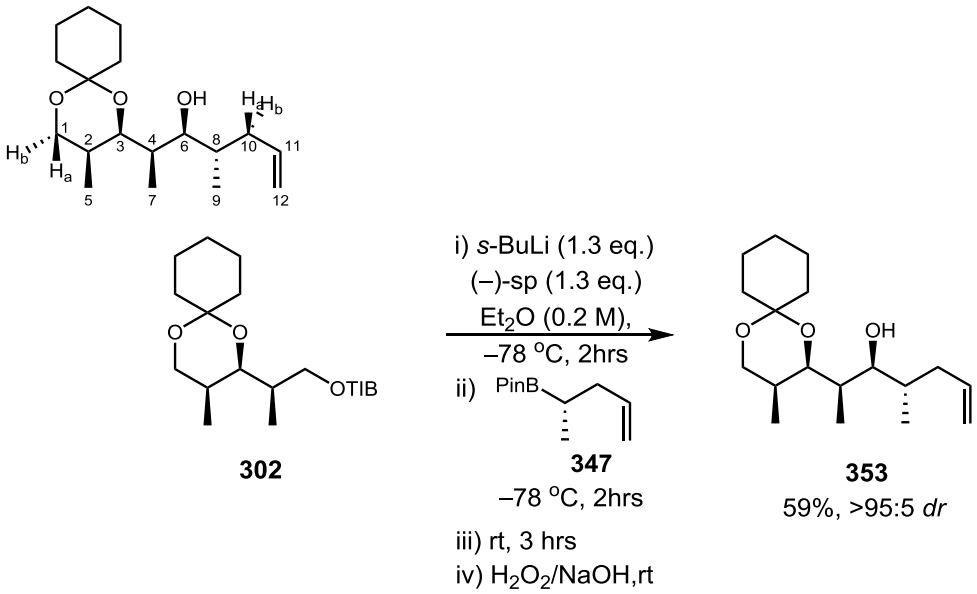
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 136.8 (11-C), 116.4 (12-C), 98.8 (O-C-O), 73.8 (O-C), 71.55 (O-C), 66.7 (1-C), 38.8 (10-C), 37.9 (Cy-$CH_2$), 36.6 (CH), 36.2 (CH), 30.3 (CH), 27.9 (Cy-$CH_2$), 25.9 (Cy-$CH_2$), 22.9 (2 × Cy-$CH_2$), 16.4 ($CH_3$), 10.7 ($CH_3$), 8.0 ($CH_3$).

**HRMS** (ESI) calc'd for $C_{18}H_{32}NaO_3$ $[M+Na]^+$: 319.2249; found: 319.2248.

$[\alpha]_D^{20}$ = –12.9 (c 0.46, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3442, 2933, 2862, 1712, 1452, 1365, 1255, 1156, 1103, 994, 959, 911, 518, 504.

**(*2R,3S,4S*)-4-methyl-2-((*2R,3S*)-3-methyl-1,5-dioxaspiro[5.5]undecan-2-yl)hept-6-en-3-ol (xx)**




To a solution of benzoate ester **302** (100 mg, 0.22 mmol) and (-)-sparteine (67.4 mg, 0.29 mmol) in dry $Et_2O$ (1.1 mL) at –78 °C was added *s*-BuLi (0.22 mL, 0.29 mmol, 1.3 M in cyclohexane/hexane = 92:8) dropwise. This mixture was stirred at –78 °C for 40 min. A solution of boronic ester **347** (56.1 mg, 0.29 mmol, 0.5 M in $Et_2O$) was added dropwise and the reaction was stirred for 2 hrs min at –78 °C. The reaction was then warmed to rt and stirred for 3 hrs. The reaction mixture was oxidized with 3 M NaOH and 30% $H_2O_2$ and stirred overnight at rt. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum,

and purified by column chromatography (ethyl acetate : petroleum ether = 1:20) to obtain compound **353** (38.5 mg, 59%).

**$R_f$**: 0.20 (ethyl acetate : petroleum ether = 1:10)

**$^1$H NMR** (400 MHz, Chloroform-d) δ 5.84 (dddd, *J* = 16.7, 10.0, 7.8, 6.5 Hz, 1H, 11-H), 5.14 – 4.99 (m, 2H, 2 × 12-H), 4.15 (dd, *J* = 11.5, 2.7 Hz, 1H, 1-H), 3.87 (dd, *J* = 10.0, 2.3 Hz, 1H, O-CH), 3.55 (dd, *J* = 10.0, 1.6 Hz, 1H, 1-H), 3.28 (dd, *J* = 9.6, 4.3 Hz, 1H, O-CH), 2.42 (m, 1H, 10-H), 2.22 (m, 1H, Cy-$CH_2$), 1.96 (m, 1H, 10-H), 1.84 – 1.73 (m, 1H, CH), 1.72 – 1.63 (m, 3H, 2 × CH, Cy-$CH_2$), 1.60 – 1.19 (m, 10H, OH, 9 × Cy-$CH_2$), 1.07 (d, *J* = 6.9 Hz, 3H, $CH_3$), 0.94 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.82 (d, *J* = 6.8 Hz, 3H, $CH_3$).

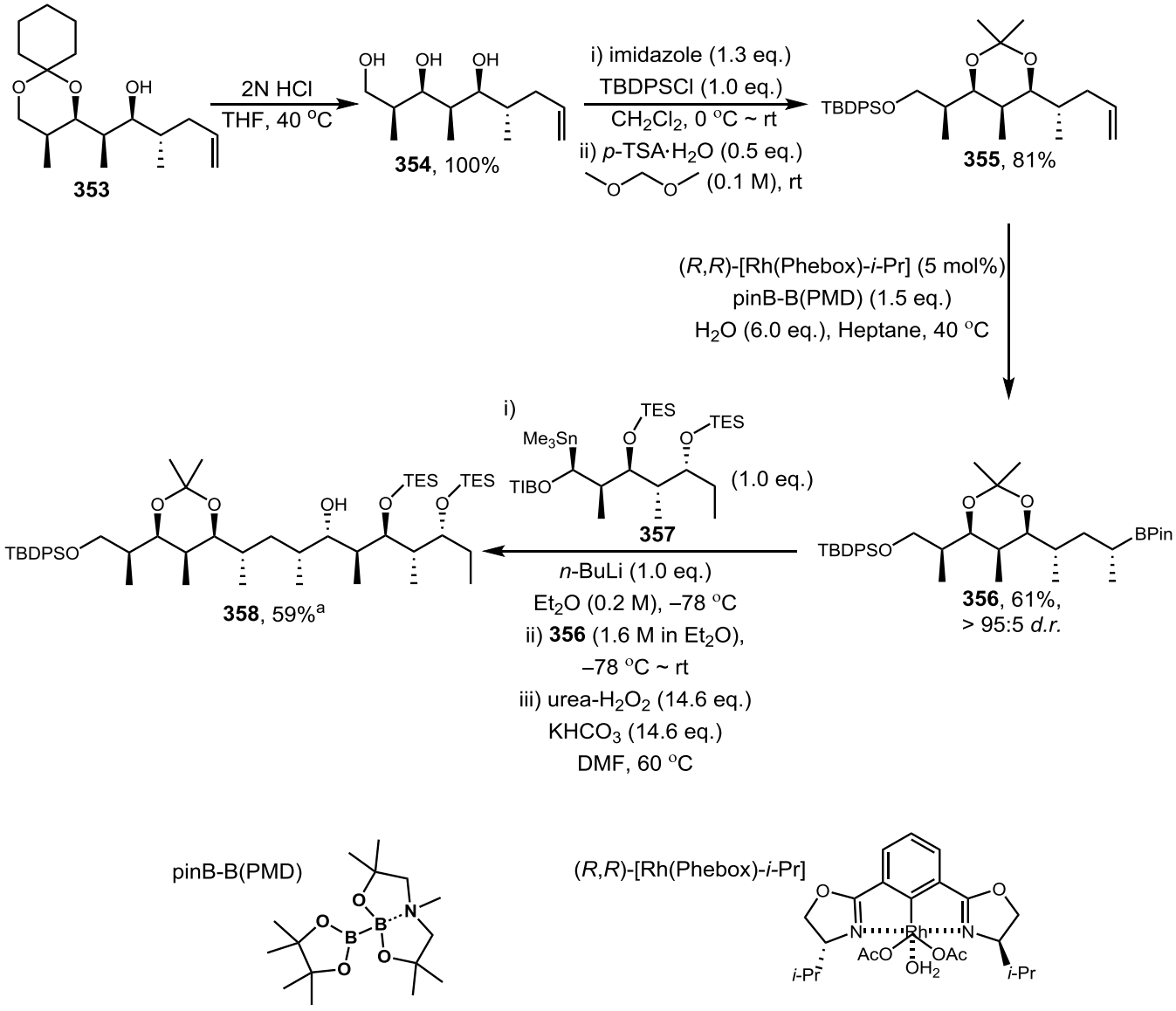
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 137.2 (11-C), 116.5 (12-C), 98.8 (O-C-O), 74.5 (O-C), 72.9 (O-C), 66.4 (1-C), 38.8 (Cy-$CH_2$), 38.4 (10-$CH_2$), 36.6 (CH), 36.2 (CH), 29.8 (CH), 27.6 (Cy-$CH_2$), 25.8 (Cy-$CH_2$), 22.7 (Cy-$CH_2$), 22.4 (Cy-$CH_2$), 15.6 ($CH_3$), 11.1 ($CH_3$), 8.2 ($CH_3$).

**HRMS** (ESI) calc'd for $C_{18}H_{32}NaO_3$ $[M+Na]^+$: 319.2249; found: 319.2251.

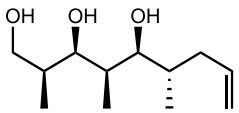
$[\alpha]_D^{20}$ = –5.4 (c 1.1, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3473,3076, 2934, 2851, 1453, 1365, 1255, 1167, 1154, 1105, 1002, 964, 910, 732, 517.

**Synthesis of Fragment 358.**




**(2S,3R,4R,5S,6S)-2,4,6-trimethylnon-8-ene-1,3,5-triol (354)**



To a solution of compound **353** (90 mg, 0.30 mmol) in THF (11.6 mL) and 2N HCl (5.5 mL) was added to mixture. The reaction was stirred vigorously at 40°C overnight. Subsequently the layers were separated, and the organic phase was extracted (5 × ethyl acetate). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica gel (ethyl acetate) to afford compound **354** (64.6 mg, 100%).

**$R_f$:** 0.11 (ethyl acetate).

**$^1$H NMR** (400 MHz, Methanol-$d_4$) δ 5.82 (dddd, *J* = 16.5, 10.1, 8.2, 6.1 Hz, 1H, C=CH), 5.08 – 4.98 (m, 2H, C=$CH_2$), 3.68 – 3.55 (m, 2H, O-$CH_2$), 3.47 (dd, *J* = 10.5, 6.2 Hz, 1H, O-CH), 3.33 (dd, *J* = 9.2, 2.5 Hz, 1H, O-CH), 2.55 – 2.46 (m, 1H, CH), 1.92 – 1.78 (m, 3H, CH + $CH_2$), 1.73 – 1.60 (m, 1H, CH), 0.96 (d, *J* = 6.5 Hz, 3H, $CH_3$), 0.94 (d, *J* = 6.6 Hz, 3H, $CH_3$), 0.84 (d, *J* = 6.7 Hz, 3H, $CH_3$).

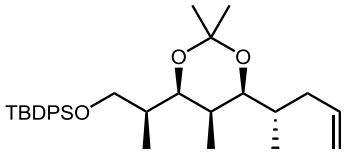
**$^{13}$C NMR** (101 MHz, Methanol-$d_4$) δ 138.5 (C=*C*H), 116.5 (C=*C*$H_2$), 78.1 (O-C), 76.7 (O-C), 66.4 (O-C), 38.6 ($CH_2$), 38.4 (CH), 38.0 (CH), 37.3 (CH), 15.8 ($CH_3$), 11.7 ($CH_3$), 7.9 ($CH_3$).

**HRMS** (ESI) calcd. for $C_{12}H_{24}NaO_3$ $[M+Na]^+$: 239.161765; found: 239.161630.

$[\alpha]_D^{22}$= +6.5 (1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3361, 2969, 2929, 2878, 2489, 1639, 1457, 1380, 1265, 183, 1030, 963, 910, 737.

**tert-butyldiphenyl((S)-2-((4R,5R,6S)-2,2,5-trimethyl-6-((S)-pent-4-en-2-yl)-1,3-dioxan-4-yl)propoxy)silane (355)**




Under an atmosphere of nitrogen compound **354** (113 mg, 0.52 mmol) was stirred in $CH_2Cl_2$ (0.52 mL) at room temperature and imidazole (45.6 mg, 0.67 mmol) was added. After cooling to 0 °C TBDPSCl (136 μL, 0.52 mmol) was added dropwise and the mixture stirred for 16 hrs at room temperature. After complete conversion $TsOH \cdot H_2O$ (49.5 mg, 0.26 mmol) and 2,2-dimethoxypropane (5.2 ml) were added at room temperature for 2 hrs. The mixture was filtered through silica and subsequently purified by flash chromatography on silica gel (pentane : ether = 25:1) to afford compound **355** (207 mg, 81%) as a colourless oil.

**$R_f$:** 0.80 (pentane : ether = 10:1).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.67 (dt, *J* = 8.0, 1.9 Hz, 4H, Ar-CH), 7.48 – 7.36 (m, 6H, Ar-CH), 5.79 (dtd, *J* = 18.0, 8.8, 5.9 Hz, 1H, C=CH), 5.08 – 4.99 (m, 2H, C=$CH_2$), 3.72 (dd, *J* = 9.6, 1.9 Hz, 1H, O-CH), 3.57 (d, *J* = 4.3 Hz, 2H, O-CH), 3.40 (dd,

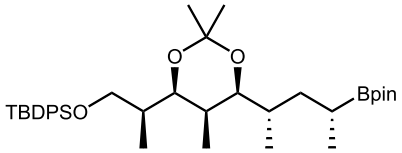
*J* = 9.9, 2.0 Hz, 1H, O-CH), 2.47 – 2.39 (m, 1H, CH), 1.94 – 1.76 (m, 2H, CH + CH), 1.64 (dddd, *J* = 13.4, 8.7, 6.9, 3.9 Hz, 2H, $CH_2$), 1.42 (s, 3H, O-C($CH_3$)$_2$-O), 1.41 (s, 3H, O-C($CH_3$)$_2$-O), 1.09 (d, *J* = 7.0 Hz, 3H, $CH_3$), 1.07 (s, 9H, C($CH_3$)$_3$), 0.78 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.75 (d, *J* = 6.8 Hz, 3H, $CH_3$).

**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 137.1 (C=*C*H), 135.7 (Ar-C), 135.7 (Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 116.3 (C=*C*$H_2$), 99.1 (O-C-O), 77.2 (O-C), 76.4 (O-C), 65.3 (O-C), 37.4 ($CH_2$), 36.9 (CH), 33.9 (CH), 31.3 (CH), 30.2 (*C*($CH_3$)$_3$), 27.0 (C(*C*$H_3$)$_3$), 19.6 ($CH_3$), 14.8 ($CH_3$), 14.0 ($CH_3$), 5.2 ($CH_3$).

**HRMS** (ESI) calcd. for $C_{31}H_{46}NaO_3Si$ $[M+Na]^+$: 517.3108; found: 517.3109.

**IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2961, 2931, 2858, 1462, 1428, 1378, 1263, 1200, 1112, 1036, 1010, 982, 910, 739, 701.

**tert-butyldiphenyl((S)-2-((4R,5R,6S)-2,2,5-trimethyl-6-((2S,4R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)-1,3-dioxan-4-yl)propoxy)silane (356)**




Under an atmosphere of argon (*R*),(*R*)-Nishiyama's catalyst (13.5 mg, 0.025 mmol), olefin **355** (247 mg, 0.50 mmol)and pinB-B(PMD) (233 mg, 0.75 mmol) were added to a Radley's tube and after 3 cycles of vacuum and argon degassed heptane (0.4 mL) was added and the mixture stirred (1400 rpm) at 40°C after which $H_2O$ (0.054 mL) and stirred for 17 hrs. Subsequently $H_2O$ (2.0 ml) and $Et_2O$ (2.0 ml) were added and the layers separated. The aqueous phase was extracted with $Et_2O$ (2 × 2.0 ml), the organic layers combined, dried over $Mg_2SO_4$, filtered and the solvent removed under reduced pressure. The obtained crude product was purified by flash chromatography on silica gel (pentane : diethyl ether = 10:1) to afford boronic ester **356** (191 mg, 61%) as a colourless oil.

**$R_f$**: 0.51 (pentane : ether = 10:1).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.65 (dt, *J* = 7.9, 1.9 Hz, 4H, Ar-CH), 7.46 – 7.35 (m, 6H, Ar-CH), 3.68 (dd, *J* = 9.7, 1.8 Hz, 1H, $OCH_2$), 3.55 (d, *J* = 4.3 Hz, 2H, OCH), 3.30 (dd, *J* = 9.7, 1.9 Hz, 1H, $OCH_2$), 1.93 (ddd, *J* = 13.5, 11.6, 2.6 Hz, 1H, CH), 1.84 –

1.74 (m, 1H, CH), 1.59 (tq, *J* = 6.7, 3.5, 2.0 Hz, 1H, CH), 1.57 – 1.48 (m, 1H, $CH_2$), 1.38 (s, 3H, O-C($CH_3$)$_2$-O), 1.37 (s, 3H, O-C($CH_3$)$_2$-O), 1.24 (s, 12H, 4 × $CH_3$-Bpin), 1.17 – 1.05 (m, 1H, $CH_2$), 1.07 (d, *J* = 7.0 Hz, 3H, $CH_3$), 1.05 (s, 9H, C($CH_3$)$_3$), 0.98 (d, *J* = 7.2 Hz, 3H, $CH_3$), 0.95 – 0.85 (m, 1H, CH), 0.75 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.72 (d, *J* = 6.8 Hz, 3H, $CH_3$).

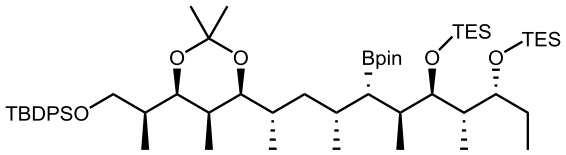
**$^{13}$C NMR** (101 MHz, Chloroform-d) δ 135.7 (Ar-C), 135.7 (Ar-C), 133.9 (Ar-C), 133.7 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 98.9 (O-C-O), 82.9 (2 × B-O-*C*($CH_3$)$_2$), 78.0 (O-C), 76.3 (O-C), 65.3 (O-C), 37.6 (CH), 36.9 (CH), 34.0 (CH), 31.3 (CH), 30.2 (*C*($CH_3$)$_3$), 27.0 (C(*C*$H_3$)$_3$), 24.9 (B-O-C(*C*$H_3$)$_2$), 24.8 (2C, B-O-C(*C*$H_3$)$_2$), 19.5 ($CH_3$), 16.9 ($CH_3$), 14.8 ($CH_3$), 5.1 ($CH_3$).

**HRMS** (ESI) calcd. for $C_{37}H_{59}BNaO_5Si$ $[M+Na]^+$: 645.412381; found: 645.411331.

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2961, 2931, 2858, 1462, 1427, 1386, 1377, 1315, 1229, 1199, 1144, 1111, 1034, 1009, 908, 864, 735, 700, 688, 615.

$[\alpha]_D^{20}$ = +8 (1.0, $CHCl_3$).

**(5R,6S,7R)-5-((2S,3S,4R,6S)-6-((4S,5R,6R)-6-((S)-1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-yl)-3,3,7,9,9-pentaethyl-6-methyl-4,8-dioxa-3,9-disilaundecane (358a)**




Under an atmosphere of nitrogen **357** (128 mg, 0.16 mmol) was stirred in $Et_2O$ (0.8 mL) at -78°C and *n*-BuLi (1.6M in hexanes, 0.1 mL, 0.16 mmol) was added dropwise and the solution was stirred for 90 min at -78°C. Subsequently a solution of **356** (100 mg, 0.16 mmol) in $Et_2O$ (0.1 mL) was added dropwise and after stirring for 30 min at –78°C the mixture was allowed to come to room temperature and stirred for 5hrs at this temperature. After completion of the reaction $H_2O$ (1.0 mL) was added, the layers separated, and the organic phase extracted with $Et_2O$ (2 × 1.0 mL). The combined organic layers were dried over $Mg_2SO_4$, filtered and the solvent was removed under pressure furnishing the crude mixture, which was purified by column chromatography

on silica gel (pentane : $CH_2Cl_2$ = 9:1) to afford compound **358a** (57.5 mg, 59% brsm) as a colourless oil.

**$R_f$:** 0.25 (pentane : $CH_2Cl_2$ = 5:1).

**$^1$H NMR** (400 MHz, Chloroform-d) δ 7.67 (dt, *J* = 7.9, 1.7 Hz, 4H, Ar-CH), 7.47 – 7.35 (m, 6H, Ar-CH), 3.81 (dt, *J* = 7.9, 4.0 Hz, 1H, OCH), 3.71 (dd, *J* = 9.7, 1.8 Hz, 1H, OCH), 3.60 – 3.52 (m, 2H, $OCH_2$), 3.37 (d, *J* = 7.8 Hz, 1H, OCH), 3.31 (dd, *J* = 9.5, 1.8 Hz, 1H, OCH), 1.96 – 1.54 (m, 8H, 6 × CH + 1 × $CH_2$), 1.38 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 1.24 (s, 12H, 4 × Bpin-$CH_3$), 1.08 (d, *J* = 6.6 Hz, 3H, $CH_3$), 1.06 (s, 9H, $C(CH_3)_3$), 0.97 (t, *J* = 8 Hz, 18H, 6 × Si-$CH_2CH_3$), 0.90 (d, *J* = 6.6 Hz, 3H, $CH_3$), 0.85 (d, *J* = 7.0 Hz, 3H, $CH_3$), 0.84 (d, *J* = 7.4 Hz, 3H, $CH_3$), 0.81 (m, 1H, CH), 0.79 (d, *J* = 6.6 Hz, 3H, $CH_3$), 0.77 (d, *J* = 6.7 Hz, 3H, $CH_3$), 0.74 – 0.66 (m, 9H, $CH_3$ + 3 × Si-$CH_2CH_3$), 0.61 (q, *J* = 8.0 Hz, 6H, 3 × Si-$CH_2CH_3$).

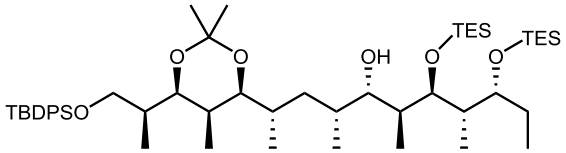
**$^{13}$C NMR** (101 MHz, Chloroform-d) 135.8 (2 × Ar-C), 135.7 (2 × Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 129.8 (2 × Ar-C), 127.8 (4 × Ar-C), 98.8 (O-C-O), 82.7 (2 × B-O-$C(CH_3)_2$), 79.7 (O-C), 78.6 (O-C), 76.4 (O-C), 73.9 (O-C), 65.3 (O-C), 41.8 ($CH_2$), 41.4 (CH), 37.0 (CH), 34.3 (CH), 31.4 (CH), 31.0 (CH), 30.2 ($O_2C(CH_3)_2$), 28.9 (CH), 28.6 ($CH_2$), 27.0 ($C(CH_3)_3$), 25.7 (2 × B-O-$C(CH_3)_2$), 25.4 (2 × B-O-$C(CH_3)_2$), 19.6 ($C(CH_3)_3$), 19.5 ($O_2C(CH_3)_2$), 17.7 ($CH_3$), 14.8 (2 × $CH_3$), 11.4 ($CH_3$), 10.8 ($CH_3$), 10.0 ($CH_3$), 7.4 (6 × Si-$CH_2CH_3$), 6.2 (3 × Si-$CH_2$), 5.8 (3 × Si-$CH_2$), 5.1 ($CH_3$).

**HRMS** (MALDI) calcd. for $C_{58}H_{105}BO_7Si_3$ $[M+H]^+$: 1031.7164; found: 1031.7175.

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2958, 2875, 1459, 1427, 1377, 1314, 1266, 1240, 1220, 1199, 1143, 1112, 1070, 1008, 970, 863, 821, 733, 700, 615.

$[\alpha]_D^{20}$ = –10 (1.0, $CHCl_3$).

**(2S,4R,5S,6S,7R,8S,9R)-2-((4S,5R,6R)-6-((S)-1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-4,6,8-trimethyl-7,9-bis((triethylsilyl)oxy)undecan-5-ol (358)**



**358a** (23.9 mg, 0024 mmol) was dissolved in DMF (0.5 mL) and urea-$H_2O_2$ (33.4 mg, 0.35 mmol) and $KHCO_3$ (35.5 mg, 0.35 mmol) were added at room temperature and the mixture was stirred vigorously in a closed vessel at 60°C for 24 hrs. After completion of the reaction $H_2O$ (0.5 mL) was added and the mixture was extracted with $Et_2O$ (2 × 1.0 ml). Subsequently the organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (pentane : diethyl ether = 25:1) to afford **358** (19.5 mg, 92%) as a colourless oil.

**$R_f$:** 0.47 (pentane : diethyl ether = 25:1).

**$^1$H NMR** (500 MHz, Chloroform-d) δ 7.68 – 7.63 (m, 4H, Ar-CH), 7.46 – 7.36 (m, 6H, Ar-CH), 4.24 – 4.17 (m, 1H, OCH), 3.78 (dt, *J* = 8.2, 4.2 Hz, 1H, OCH), 3.70 (dd, *J* = 9.6, 1.9 Hz, 1H, OCH), 3.57 – 3.54 (m, 2H, $OCH_2$), 3.49 (d, *J* = 10.1 Hz, 1H, OCH), 3.35 (dd, *J* = 9.9, 2.0 Hz, 1H, OCH), 2.60 (s, 1H, OH), 1.78 (m, 1H, CH), 1.73 – 1.52 (m, 10H, 6 × CH + 2 × $CH_2$), 1.42 (s, 3H, $CH_3$), 1.39 (s, 3H, $CH_3$), 1.07 (d, *J* = 6.7 Hz, 3H, $CH_3$), 1.06 (s, 9H, $C(CH_3)_3$), 0.96 (t, *J* = 8.0 Hz, 18H, 6 × Si-$CH_2C\mathit{H}_3$), 0.86 – 0.78 (m, 12H, 4 × $CH_3$), 0.75 (d, *J* = 6.8 Hz, 6H, 2 × $CH_3$), 0.64 (q, *J* = 8.0 Hz, 6H, 3 × Si-$C\mathit{H}_2CH_3$), 0.60 (q, *J* = 7.8 Hz, 6H, 3 × Si-$C\mathit{H}_2CH_3$).

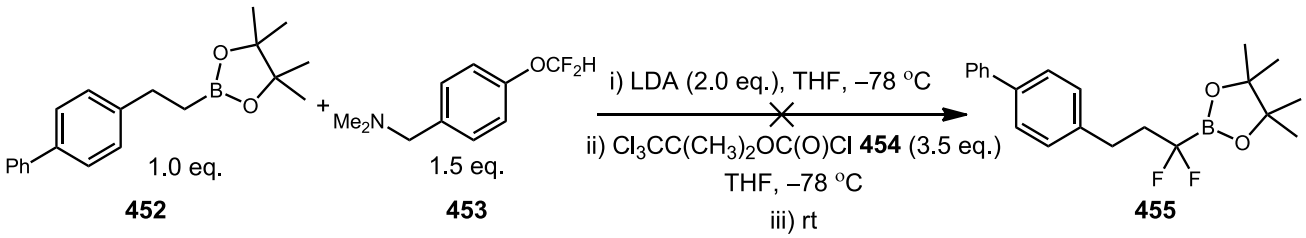
**$^{13}$C NMR** (126 MHz, Chloroform-d) δ 135.8 (2 × Ar-C), 135.7 (2 × Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 129.8 (2 × Ar-C), 127.8 (4 × Ar-C), 99.4 (O-C-O), 79.3 (O-C), 76.3 (O-C), 74.3 (O-C), 72.6 (O-C), 70.8 (O-C), 65.2 (O-C), 41.6 ($CH_2$), 39.2 (CH), 37.8 (CH), 36.8 (CH), 32.1 (CH), 31.4 (CH), 30.6 ($CH_3$), 29.9 ($O_2C(\mathit{C}H_3)_2$), 28.2 ($CH_2$), 27.0 ($C(\mathit{C}H_3)_3$), 19.7 ($\mathit{C}(CH_3)_3$), 19.5 ($O_2C(\mathit{C}H_3)_2$), 16.2 ($CH_3$), 14.8 (2 × $CH_3$), 13.8 ($CH_3$), 10.5 ($CH_3$), 9.7 ($CH_3$), 7.4 (3 × $CH_3$), 7.3 (3 × $CH_3$), 6.1 (3 × Si-$CH_2$), 5.9 (3 × Si-$CH_2$), 5.0 ($CH_3$).

**HRMS** (ESI) calcd. for $C_{52}H_{95}O_6Si_3$ $[M+H]^+$: 899.643097; found: 899.641513.

$[\alpha]_D^{22}$= –8 (1.0, $CHCl_3$).

**IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3497, 3071, 2957, 2935, 2875, 1460, 1427, 1414, 1263, 1215, 1200, 1184, 1150, 1110, 1069, 1008, 976, 821, 757, 737.

**General procedure for exploration of difluoromethylation/monofluoromethylation reactions of organoboronic ester**




To a solution of boronic ester **452** (61.6 mg, 0.2 mmol) and difluoromethyl aryl ether **453** (60.4 mg, 0.3 mmol) in THF (1.5 mL) was added a freshly prepared solution of LDA (0.4 mmol) in THF (0.5 mL) dropwise at −78 °C under $N_2$ atmosphere. The reaction was stirred for 1.0 hr at −78 °C before addition of acyl chloride **454** (167 mg, 0.7 mmol). The reaction mixture was stirred for additional 1.0 hr at −78 °C, and subsequently stirred for another 1.0 hr at room temperature. Water was added, the reaction was extracted with diethyl ether (×3), dried over $MgSO_4$, filtered and concentrated under vacuum to give the crude mixture.

**Note**:

1. Various difluoromethylating/monofluoromethylating reagents, bsaes, solvents, and N-activatiors were screend.
2. The reagents amounts were also investigated.
3. Different reaction time of deprotonation, borylation, N-activation, and 1,2-migration was also examined.
4. The 1,2-migration step was attempted at different temperatures (room temperature or reflux)

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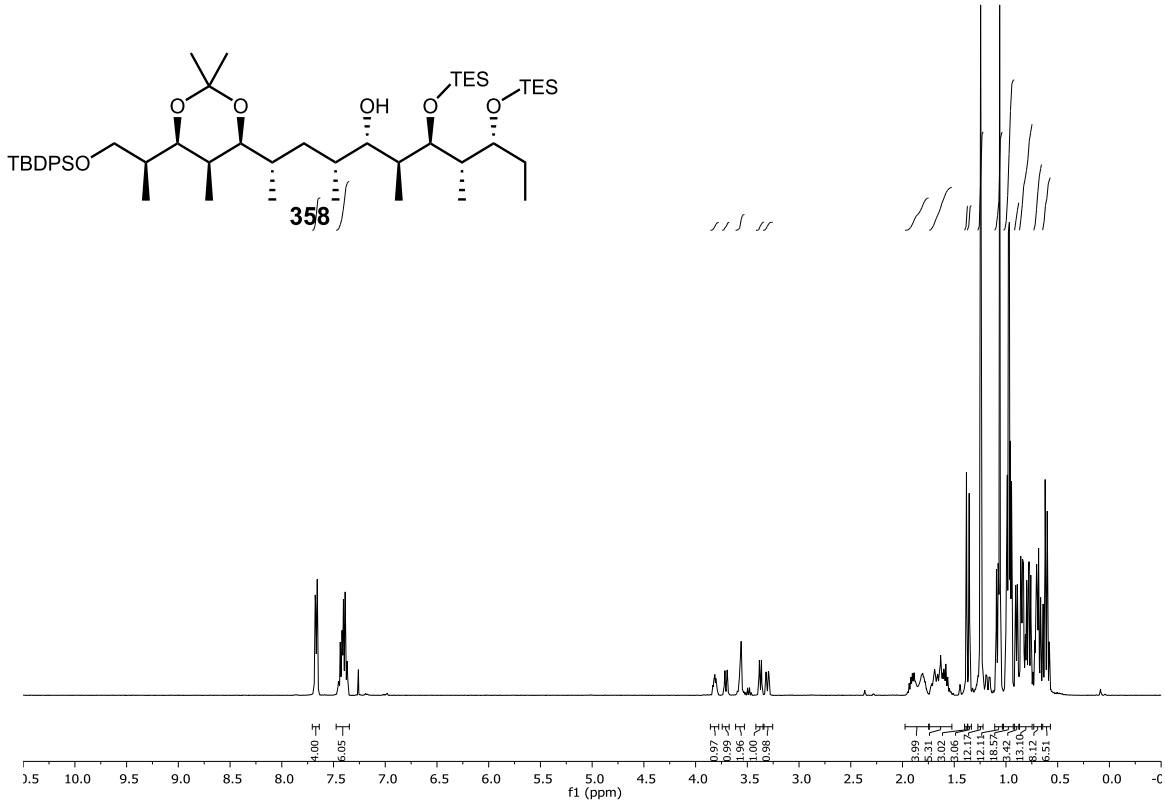
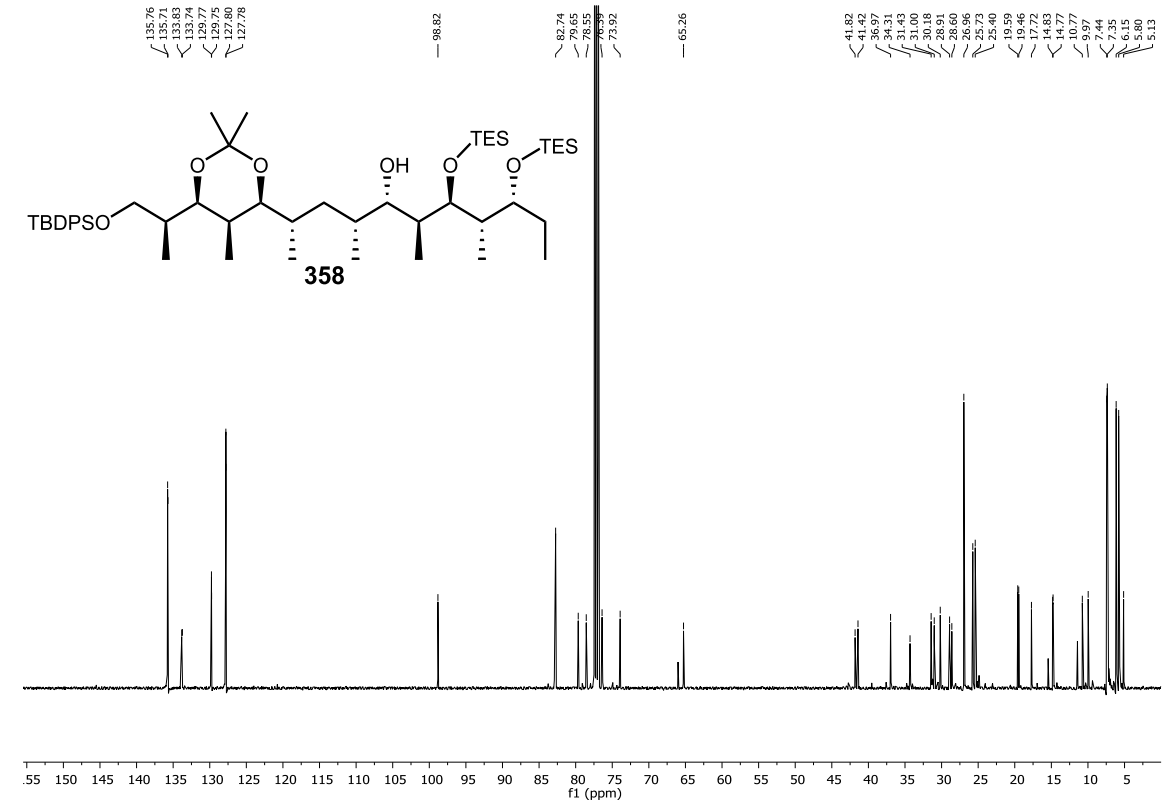
# 6. Appendix




**$^{11}$H NMR** spectrum of fragment **358**




**$^{13}$C NMR** spectrum of fragment **358**